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# R.1

**R.1.1**

**R.1.1.1**

**R.1.1.1.1**

R.1.1.1.1 Mortality endpoints

**R.1.1.1.1.1**

R.1.1.1.1.1 Time to all-cause mortality

Table R.1.1.1.1.1: 1 Cox Regression for time to all-cause mortality overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 167 | 5.1 | 2.58 | 3304 | 148 | 4.5 | 2.28 | 0.87 | (0.70,1.08) | 0.2137 | |
| Sex | | | | | | | | | | | | 0.7382 |
| Male | 2210 | 122 | 5.5 | 2.81 | 2207 | 109 | 4.9 | 2.51 | 0.89 | (0.69,1.15) | 0.3725 | |
| Female | 1095 | 45 | 4.1 | 2.10 | 1097 | 39 | 3.6 | 1.81 | 0.82 | (0.53,1.25) | 0.3537 | |
| Age [years] | | | | | | | | | | | | 0.4337 |
| <65 | 1501 | 27 | 1.8 | 0.93 | 1501 | 29 | 1.9 | 0.99 | 1.06 | (0.63,1.79) | 0.8230 | |
| >=65 | 1804 | 140 | 7.8 | 3.92 | 1803 | 119 | 6.6 | 3.33 | 0.84 | (0.66,1.08) | 0.1698 | |
| Region | | | | | | | | | | | | 0.8807 |
| North America | 873 | 54 | 6.2 | 3.30 | 844 | 50 | 5.9 | 3.11 | 0.92 | (0.63,1.35) | 0.6688 | |
| Europe | 1304 | 80 | 6.1 | 2.96 | 1344 | 70 | 5.2 | 2.53 | 0.84 | (0.61,1.15) | 0.2758 | |
| Japan | 308 | 7 | 2.3 | 1.08 | 304 | 7 | 2.3 | 1.11 | 1.22 | (0.43,3.48) | 0.7091 | |
| Other Asia | 820 | 26 | 3.2 | 1.74 | 812 | 21 | 2.6 | 1.41 | 0.78 | (0.44,1.39) | 0.4032 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2396 |
| Diabetic | 1515 | 123 | 8.1 | 4.05 | 1525 | 101 | 6.6 | 3.29 | 0.80 | (0.61,1.04) | 0.0918 | |
| Non-diabetic | 1790 | 44 | 2.5 | 1.28 | 1779 | 47 | 2.6 | 1.37 | 1.07 | (0.71,1.61) | 0.7508 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9911 |
| <30 | 1961 | 83 | 4.2 | 2.20 | 1955 | 71 | 3.6 | 1.88 | 0.86 | (0.63,1.19) | 0.3640 | |
| >=30 | 1337 | 84 | 6.3 | 3.11 | 1340 | 76 | 5.7 | 2.82 | 0.87 | (0.63,1.18) | 0.3621 | |
| Prior CV disease | | | | | | | | | | | | 0.9240 |
| No | 2401 | 77 | 3.2 | 1.63 | 2443 | 72 | 2.9 | 1.50 | 0.89 | (0.65,1.23) | 0.4843 | |
| Yes | 904 | 90 | 10.0 | 5.08 | 861 | 76 | 8.8 | 4.47 | 0.87 | (0.64,1.18) | 0.3820 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0407 |
| <130 | 1208 | 54 | 4.5 | 2.28 | 1190 | 60 | 5.0 | 2.58 | 1.19 | (0.82,1.71) | 0.3625 | |
| >=130 | 2097 | 113 | 5.4 | 2.74 | 2114 | 88 | 4.2 | 2.11 | 0.73 | (0.55,0.97) | 0.0287 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.1.1: 1 Cox Regression for time to all-cause mortality overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.0386 |
| <75 | 1286 | 88 | 6.8 | 3.47 | 1294 | 100 | 7.7 | 3.87 | 1.10 | (0.82,1.46) | 0.5237 | |
| 75 to <85 | 1033 | 49 | 4.7 | 2.39 | 1019 | 28 | 2.7 | 1.39 | 0.58 | (0.37,0.93) | 0.0226 | |
| >=85 | 986 | 30 | 3.0 | 1.58 | 991 | 20 | 2.0 | 1.05 | 0.64 | (0.36,1.13) | 0.1226 | |
| History of heart failure | | | | | | | | | | | | 0.0750 |
| No | 2970 | 134 | 4.5 | 2.30 | 2979 | 107 | 3.6 | 1.83 | 0.78 | (0.60,1.01) | 0.0552 | |
| Yes | 334 | 33 | 9.9 | 4.99 | 324 | 41 | 12.7 | 6.46 | 1.26 | (0.79,1.99) | 0.3304 | |
| History of renal disease | | | | | | | | | | | | 0.2944 |
| Diabetic kidney disease | 1025 | 88 | 8.6 | 4.29 | 1032 | 71 | 6.9 | 3.43 | 0.78 | (0.57,1.07) | 0.1251 | |
| Glomerular disease | 816 | 10 | 1.2 | 0.65 | 853 | 5 | 0.6 | 0.31 | 0.48 | (0.16,1.40) | 0.1797 | |
| Hypertensive/renovascular disease | 739 | 33 | 4.5 | 2.31 | 706 | 30 | 4.2 | 2.13 | 0.88 | (0.54,1.44) | 0.6104 | |
| Other/Unknown | 725 | 36 | 5.0 | 2.46 | 713 | 42 | 5.9 | 3.00 | 1.21 | (0.77,1.89) | 0.4043 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.7652 |
| <30 | 1151 | 92 | 8.0 | 4.07 | 1131 | 79 | 7.0 | 3.53 | 0.86 | (0.63,1.16) | 0.3100 | |
| 30 to <45 | 1461 | 65 | 4.4 | 2.24 | 1467 | 62 | 4.2 | 2.14 | 0.95 | (0.67,1.35) | 0.7729 | |
| >=45 | 693 | 10 | 1.4 | 0.76 | 706 | 7 | 1.0 | 0.51 | 0.67 | (0.25,1.75) | 0.4113 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.5721 |
| Normal (<30) | 663 | 36 | 5.4 | 2.70 | 665 | 33 | 5.0 | 2.50 | 0.94 | (0.59,1.51) | 0.7932 | |
| Microalbuminuria (30 to <=300) | 937 | 59 | 6.3 | 3.20 | 927 | 58 | 6.3 | 3.16 | 0.97 | (0.68,1.40) | 0.8731 | |
| Macroalbuminuria (>300) | 1705 | 72 | 4.2 | 2.18 | 1712 | 57 | 3.3 | 1.70 | 0.75 | (0.53,1.07) | 0.1094 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5807 |
| Low, moderate or high | 833 | 20 | 2.4 | 1.22 | 839 | 20 | 2.4 | 1.23 | 1.03 | (0.55,1.91) | 0.9373 | |
| Very high | 2472 | 147 | 5.9 | 3.03 | 2465 | 128 | 5.2 | 2.63 | 0.85 | (0.67,1.08) | 0.1800 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.1668 |
| No | 508 | 44 | 8.7 | 4.63 | 473 | 27 | 5.7 | 3.03 | 0.65 | (0.40,1.05) | 0.0770 | |
| Yes | 2797 | 123 | 4.4 | 2.22 | 2831 | 121 | 4.3 | 2.16 | 0.95 | (0.74,1.22) | 0.6905 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.1.1: 1 Cox Regression for time to all-cause mortality overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.1062 |
| No | 1940 | 61 | 3.1 | 1.62 | 1908 | 63 | 3.3 | 1.70 | 1.08 | (0.76,1.54) | 0.6617 | |
| Yes | 1365 | 106 | 7.8 | 3.91 | 1396 | 85 | 6.1 | 3.05 | 0.74 | (0.56,0.99) | 0.0426 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3769 |
| No | 1852 | 49 | 2.6 | 1.37 | 1942 | 54 | 2.8 | 1.44 | 1.02 | (0.69,1.50) | 0.9260 | |
| Yes | 1453 | 118 | 8.1 | 4.04 | 1362 | 94 | 6.9 | 3.41 | 0.82 | (0.63,1.08) | 0.1593 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.1.1: 1**

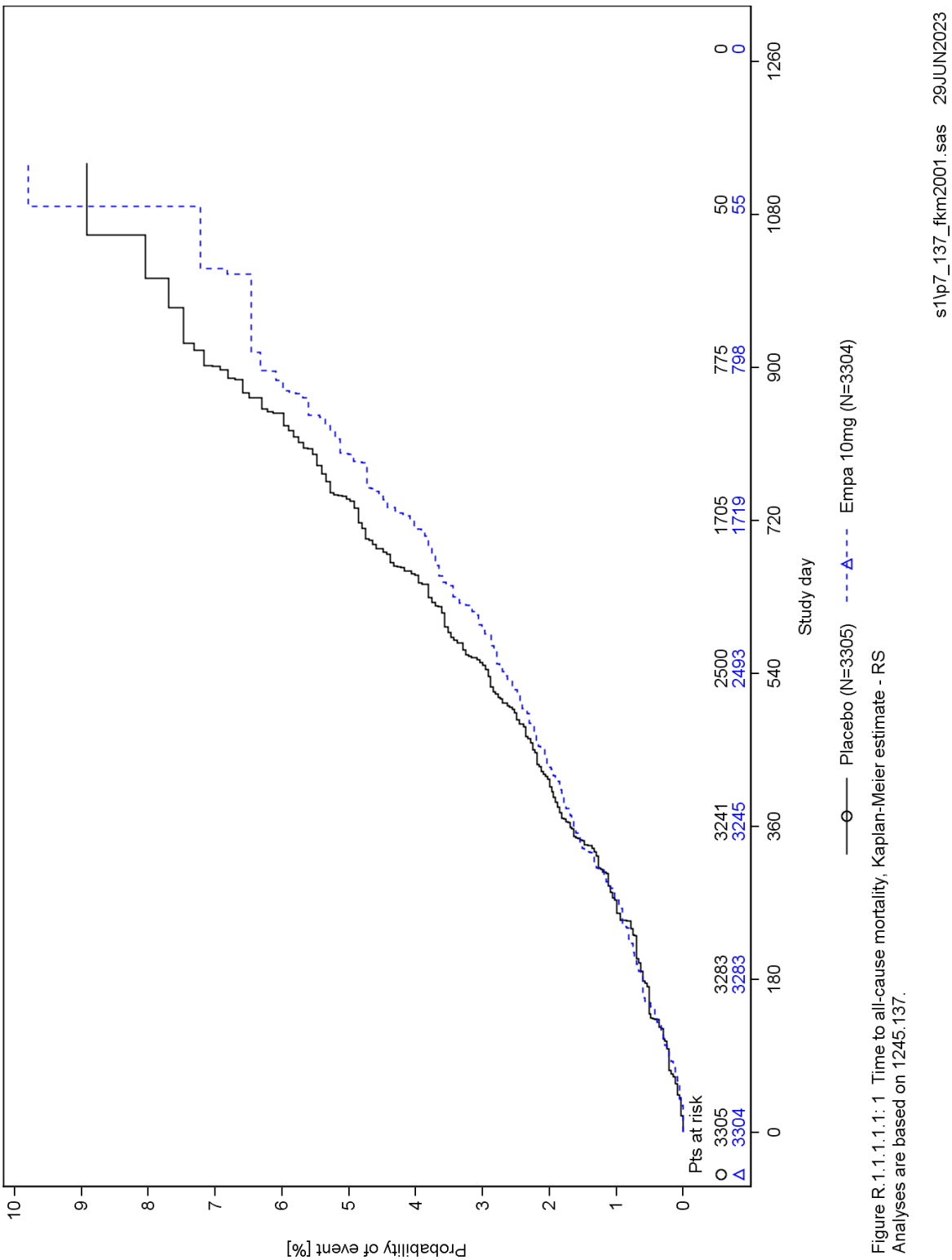


Figure R.1.1.1.1.1: 1 Time to all-cause mortality, Kaplan-Meier estimate - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.1.1: 2**

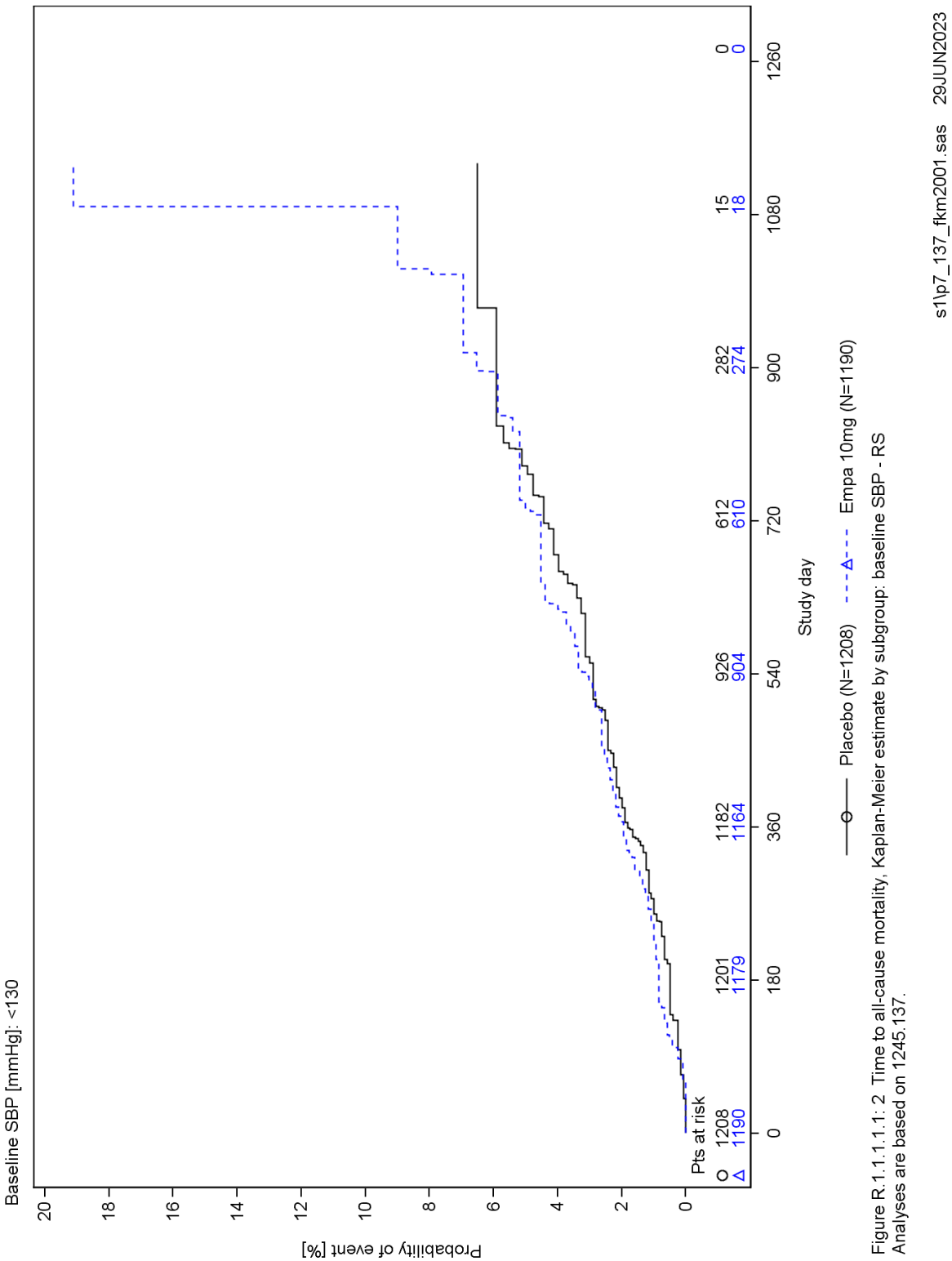


Figure R.1.1.1.1.1: 2 Time to all-cause mortality, Kaplan-Meier estimate by subgroup: baseline SBP - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.1.1: 2**

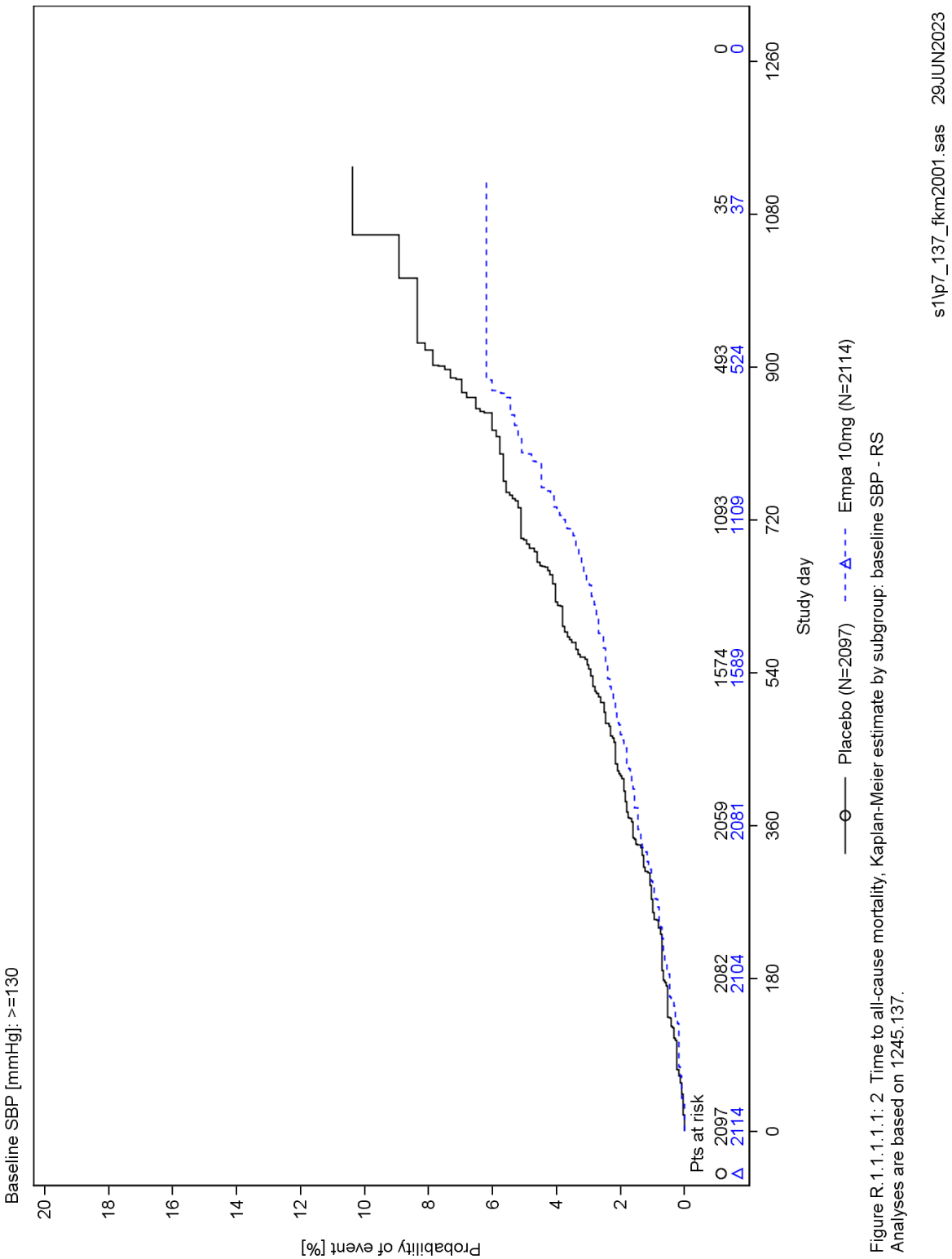


Figure R.1.1.1.1.1: 2 Time to all-cause mortality, Kaplan-Meier estimate by subgroup: baseline SBP - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.1.1: 3**

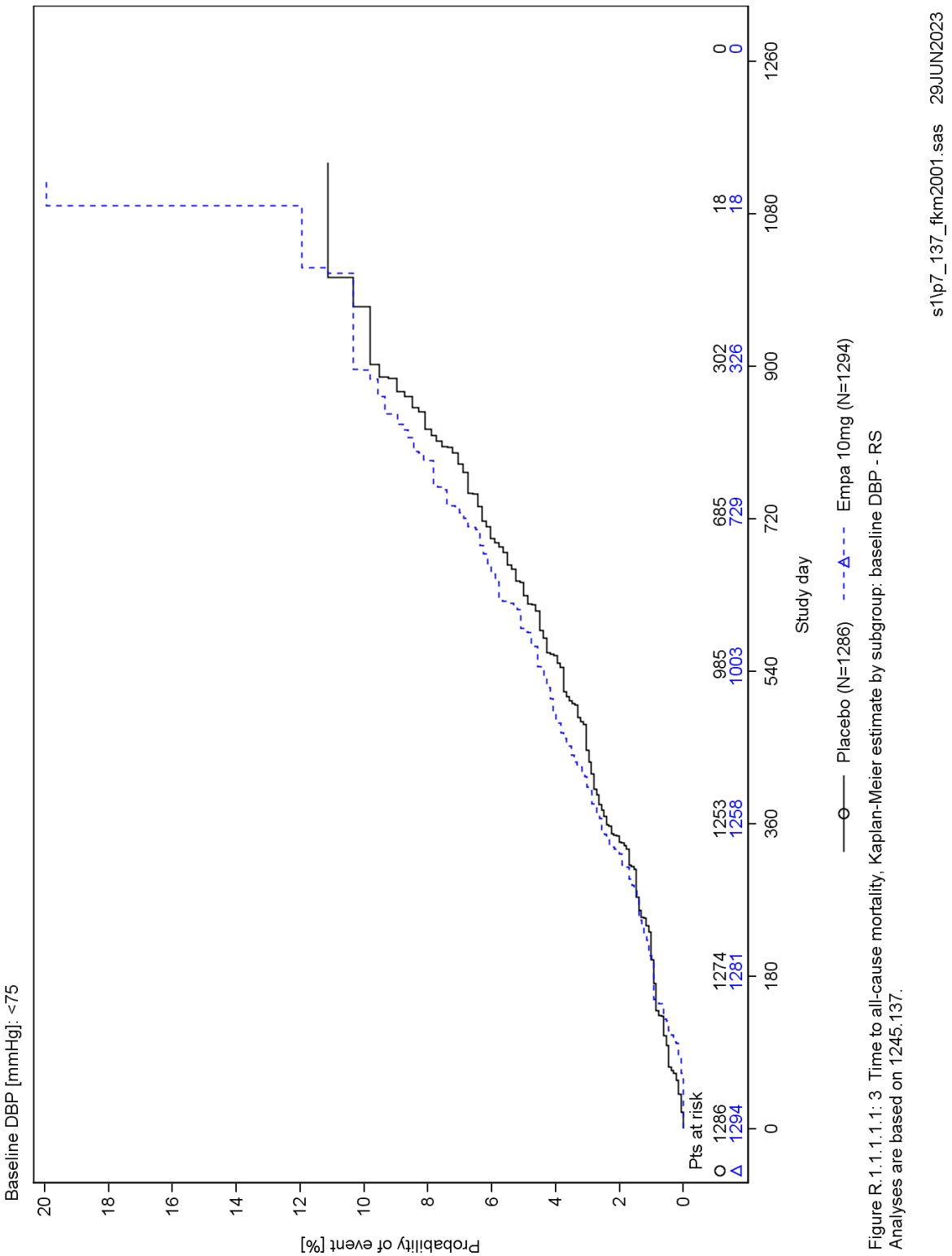


Figure R.1.1.1.1.1: 3 Time to all-cause mortality, Kaplan-Meier estimate by subgroup: baseline DBP - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.1.1: 3**

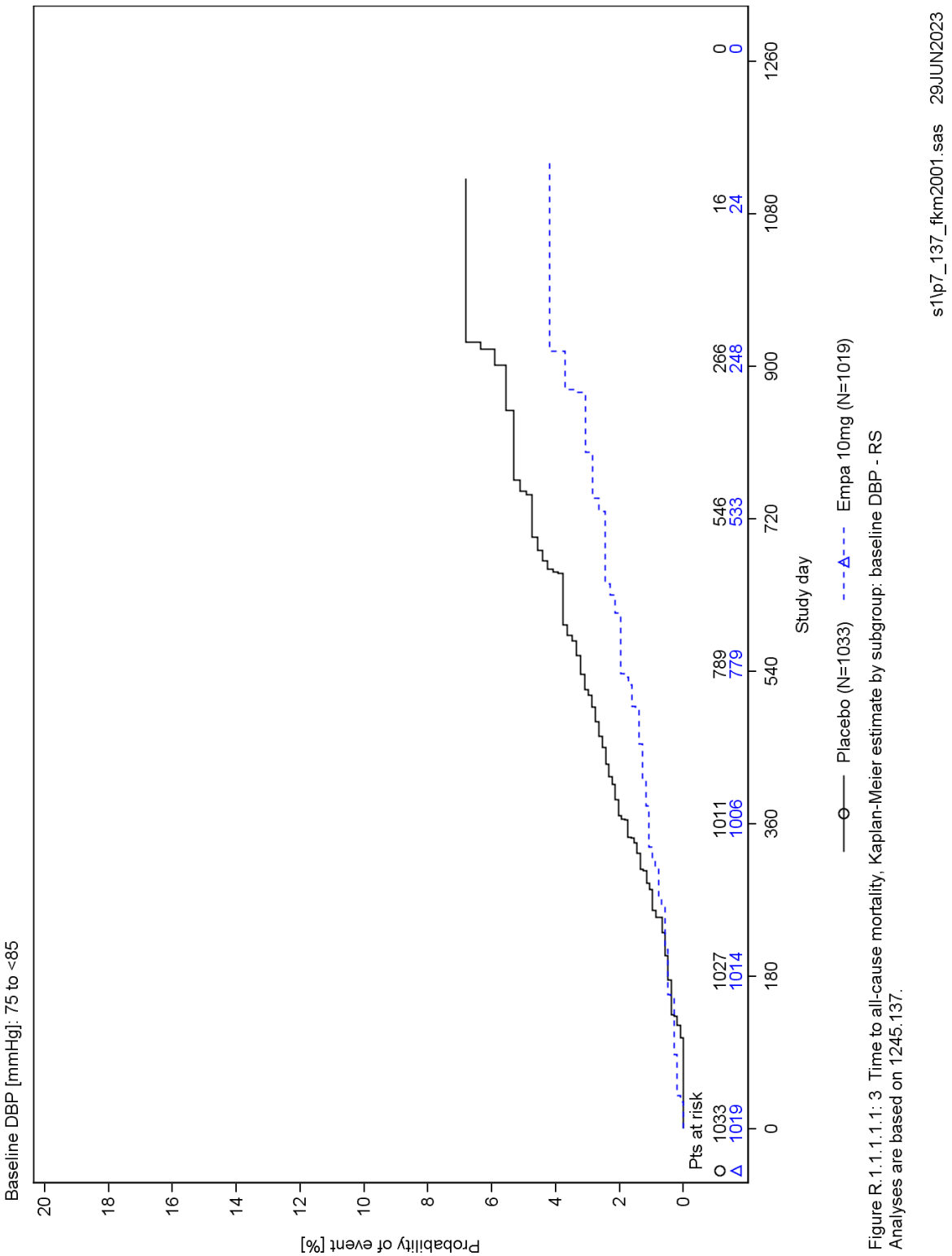


Figure R.1.1.1.1.1: 3 Time to all-cause mortality, Kaplan-Meier estimate by subgroup: baseline DBP - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.1.1: 3**

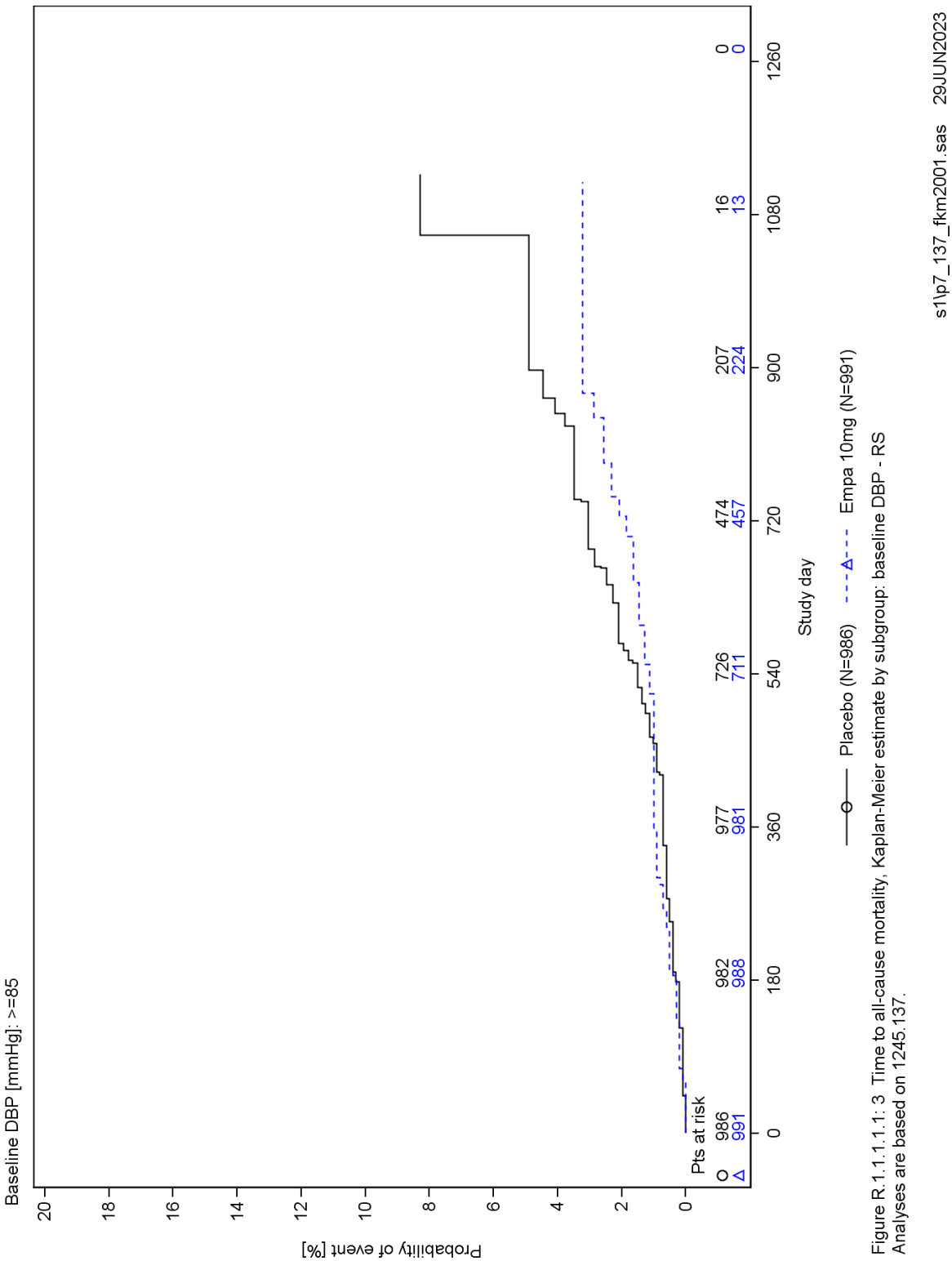


Figure R.1.1.1.1.1: 3 Time to all-cause mortality, Kaplan-Meier estimate by subgroup: baseline DBP - RS
Analyses are based on 1245.137.

**R.1.1.1.1.2**

R.1.1.1.1.2 Time to adjudicated CV death

Table R.1.1.1.1.2: 1 Cox Regression for time to adjudicated CV death overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 69 | 2.1 | 1.06 | 3304 | 59 | 1.8 | 0.91 | 0.84 | (0.60, 1.19) | 0.3366 | |
| Sex | | | | | | | | | | | | 0.5777 |
| Male | 2210 | 49 | 2.2 | 1.13 | 2207 | 44 | 2.0 | 1.01 | 0.90 | (0.60, 1.35) | 0.5976 | |
| Female | 1095 | 20 | 1.8 | 0.93 | 1097 | 15 | 1.4 | 0.70 | 0.72 | (0.37, 1.40) | 0.3307 | |
| Age [years] | | | | | | | | | | | | 0.7112 |
| <65 | 1501 | 11 | 0.7 | 0.38 | 1501 | 11 | 0.7 | 0.38 | 0.98 | (0.42, 2.26) | 0.9621 | |
| >=65 | 1804 | 58 | 3.2 | 1.62 | 1803 | 48 | 2.7 | 1.34 | 0.82 | (0.56, 1.21) | 0.3203 | |
| Region | | | | | | | | | | | | 0.6377 |
| North America | 873 | 24 | 2.7 | 1.47 | 844 | 20 | 2.4 | 1.25 | 0.84 | (0.46, 1.51) | 0.5556 | |
| Europe | 1304 | 36 | 2.8 | 1.33 | 1344 | 30 | 2.2 | 1.08 | 0.80 | (0.49, 1.30) | 0.3764 | |
| Japan | 308 | 1 | 0.3 | 0.15 | 304 | 3 | 1.0 | 0.48 | 3.62 | (0.38,34.83) | 0.2648 | |
| Other Asia | 820 | 8 | 1.0 | 0.53 | 812 | 6 | 0.7 | 0.40 | 0.73 | (0.25, 2.12) | 0.5680 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.0774 |
| Diabetic | 1515 | 58 | 3.8 | 1.91 | 1525 | 42 | 2.8 | 1.37 | 0.71 | (0.48, 1.06) | 0.0913 | |
| Non-diabetic | 1790 | 11 | 0.6 | 0.32 | 1779 | 17 | 1.0 | 0.50 | 1.54 | (0.72, 3.28) | 0.2671 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0022 |
| <30 | 1961 | 20 | 1.0 | 0.53 | 1955 | 32 | 1.6 | 0.85 | 1.62 | (0.93, 2.84) | 0.0903 | |
| >=30 | 1337 | 49 | 3.7 | 1.81 | 1340 | 26 | 1.9 | 0.96 | 0.51 | (0.32, 0.83) | 0.0061 | |
| Prior CV disease | | | | | | | | | | | | 0.5027 |
| No | 2401 | 24 | 1.0 | 0.51 | 2443 | 25 | 1.0 | 0.52 | 1.00 | (0.57, 1.75) | 0.9976 | |
| Yes | 904 | 45 | 5.0 | 2.54 | 861 | 34 | 3.9 | 2.00 | 0.78 | (0.50, 1.22) | 0.2833 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0357 |
| <130 | 1208 | 21 | 1.7 | 0.89 | 1190 | 27 | 2.3 | 1.16 | 1.37 | (0.78, 2.43) | 0.2759 | |
| >=130 | 2097 | 48 | 2.3 | 1.17 | 2114 | 32 | 1.5 | 0.77 | 0.63 | (0.40, 0.99) | 0.0439 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.1.2: 1 Cox Regression for time to adjudicated CV death overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.0259 |
| <75 | 1286 | 35 | 2.7 | 1.38 | 1294 | 44 | 3.4 | 1.70 | 1.23 | (0.79, 1.92) | 0.3644 | |
| 75 to <85 | 1033 | 19 | 1.8 | 0.93 | 1019 | 9 | 0.9 | 0.45 | 0.49 | (0.22, 1.07) | 0.0746 | |
| >=85 | 986 | 15 | 1.5 | 0.79 | 991 | 6 | 0.6 | 0.32 | 0.38 | (0.15, 0.98) | 0.0453 | |
| History of heart failure | | | | | | | | | | | | 0.2378 |
| No | 2970 | 52 | 1.8 | 0.89 | 2979 | 39 | 1.3 | 0.67 | 0.74 | (0.49, 1.12) | 0.1539 | |
| Yes | 334 | 17 | 5.1 | 2.57 | 324 | 20 | 6.2 | 3.15 | 1.18 | (0.61, 2.25) | 0.6250 | |
| History of renal disease | | | | | | | | | | | | 0.1376 |
| Diabetic kidney disease | 1025 | 42 | 4.1 | 2.05 | 1032 | 28 | 2.7 | 1.35 | 0.65 | (0.40, 1.05) | 0.0808 | |
| Glomerular disease | 816 | 3 | 0.4 | 0.19 | 853 | 2 | 0.2 | 0.12 | 0.62 | (0.10, 3.73) | 0.6056 | |
| Hypertensive/renovascular disease | 739 | 15 | 2.0 | 1.05 | 706 | 12 | 1.7 | 0.85 | 0.77 | (0.36, 1.66) | 0.5108 | |
| Other/Unknown | 725 | 9 | 1.2 | 0.62 | 713 | 17 | 2.4 | 1.22 | 1.98 | (0.88, 4.44) | 0.0985 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6189 |
| <30 | 1151 | 34 | 3.0 | 1.50 | 1131 | 29 | 2.6 | 1.30 | 0.85 | (0.52, 1.40) | 0.5302 | |
| 30 to <45 | 1461 | 33 | 2.3 | 1.14 | 1467 | 26 | 1.8 | 0.90 | 0.78 | (0.47, 1.31) | 0.3476 | |
| >=45 | 693 | 2 | 0.3 | 0.15 | 706 | 4 | 0.6 | 0.29 | 1.89 | (0.35,10.34) | 0.4604 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.6894 |
| Normal (<30) | 663 | 14 | 2.1 | 1.05 | 665 | 15 | 2.3 | 1.14 | 1.11 | (0.53, 2.30) | 0.7830 | |
| Microalbuminuria (30 to <=300) | 937 | 29 | 3.1 | 1.57 | 927 | 22 | 2.4 | 1.20 | 0.75 | (0.43, 1.30) | 0.3073 | |
| Macroalbuminuria (>300) | 1705 | 26 | 1.5 | 0.79 | 1712 | 22 | 1.3 | 0.66 | 0.80 | (0.45, 1.41) | 0.4451 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0822 |
| Low, moderate or high | 833 | 5 | 0.6 | 0.31 | 839 | 10 | 1.2 | 0.61 | 2.04 | (0.70, 5.98) | 0.1922 | |
| Very high | 2472 | 64 | 2.6 | 1.32 | 2465 | 49 | 2.0 | 1.01 | 0.75 | (0.51, 1.08) | 0.1224 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.4994 |
| No | 508 | 16 | 3.1 | 1.68 | 473 | 10 | 2.1 | 1.12 | 0.66 | (0.30, 1.46) | 0.3093 | |
| Yes | 2797 | 53 | 1.9 | 0.96 | 2831 | 49 | 1.7 | 0.87 | 0.90 | (0.61, 1.33) | 0.5909 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.1.2: 1 Cox Regression for time to adjudicated CV death overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5005 |
| No | 1940 | 21 | 1.1 | 0.56 | 1908 | 20 | 1.0 | 0.54 | 0.99 | (0.54, 1.83) | 0.9798 | |
| Yes | 1365 | 48 | 3.5 | 1.77 | 1396 | 39 | 2.8 | 1.40 | 0.77 | (0.50, 1.17) | 0.2213 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.4703 |
| No | 1852 | 18 | 1.0 | 0.50 | 1942 | 20 | 1.0 | 0.53 | 1.04 | (0.55, 1.97) | 0.9039 | |
| Yes | 1453 | 51 | 3.5 | 1.75 | 1362 | 39 | 2.9 | 1.42 | 0.79 | (0.52, 1.19) | 0.2568 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.1.2: 1**

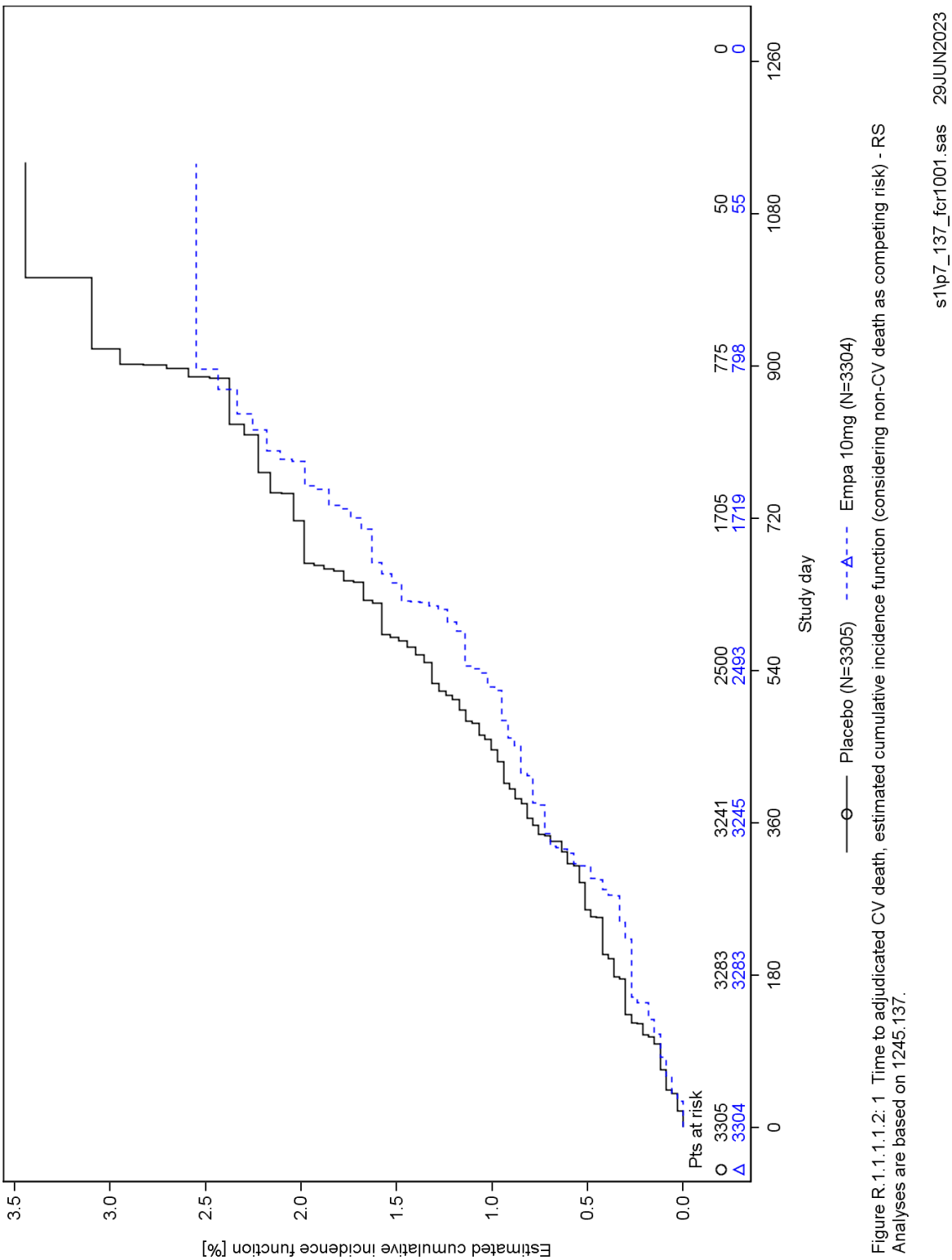


Figure R.1.1.1.1.2: 1 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.1.2: 2**

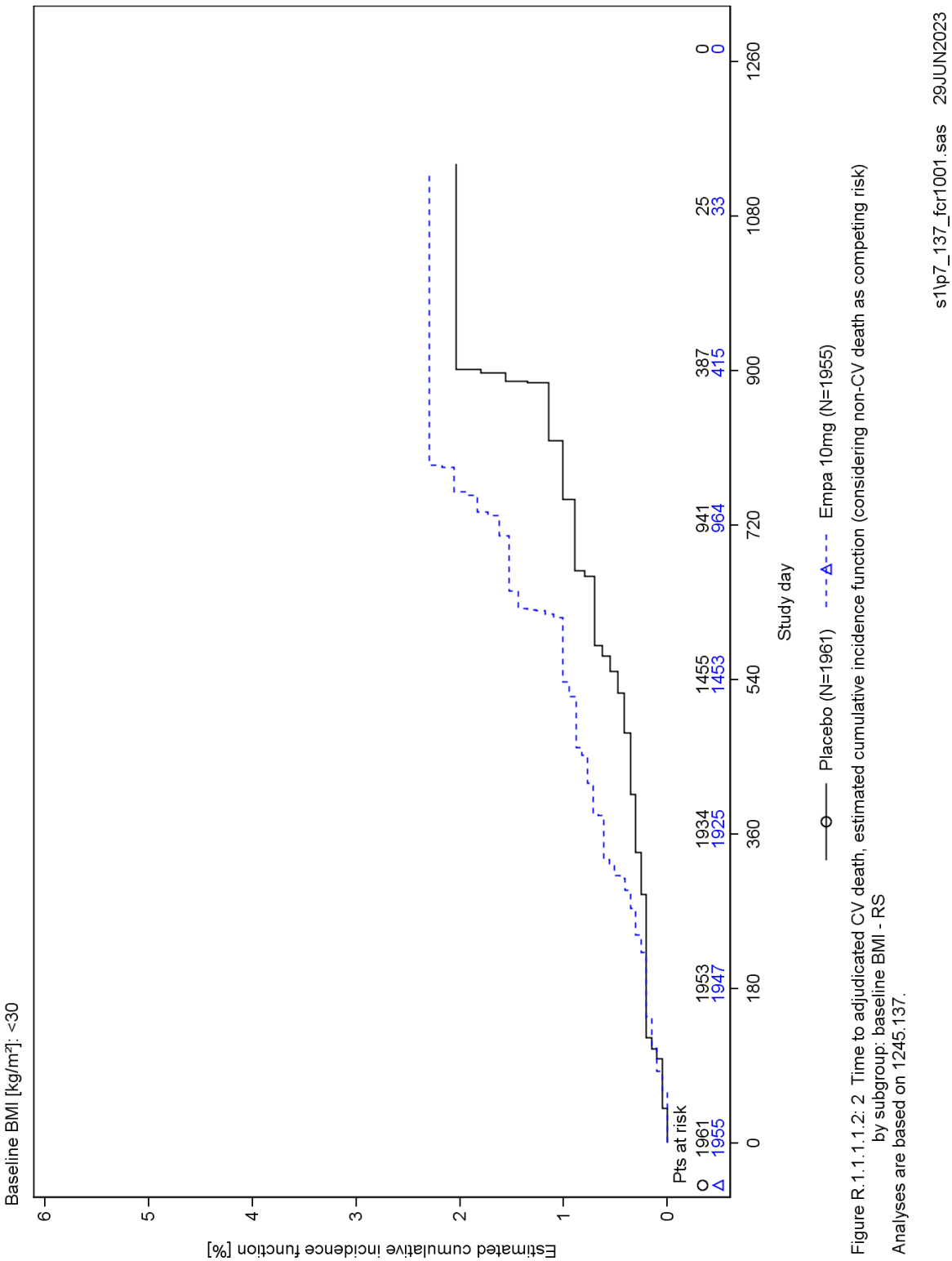


Figure R.1.1.1.1.2: 2 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) by subgroup: baseline BMI - RS

Analyses are based on 1245.137.

**Figure R.1.1.1.1.2: 2**

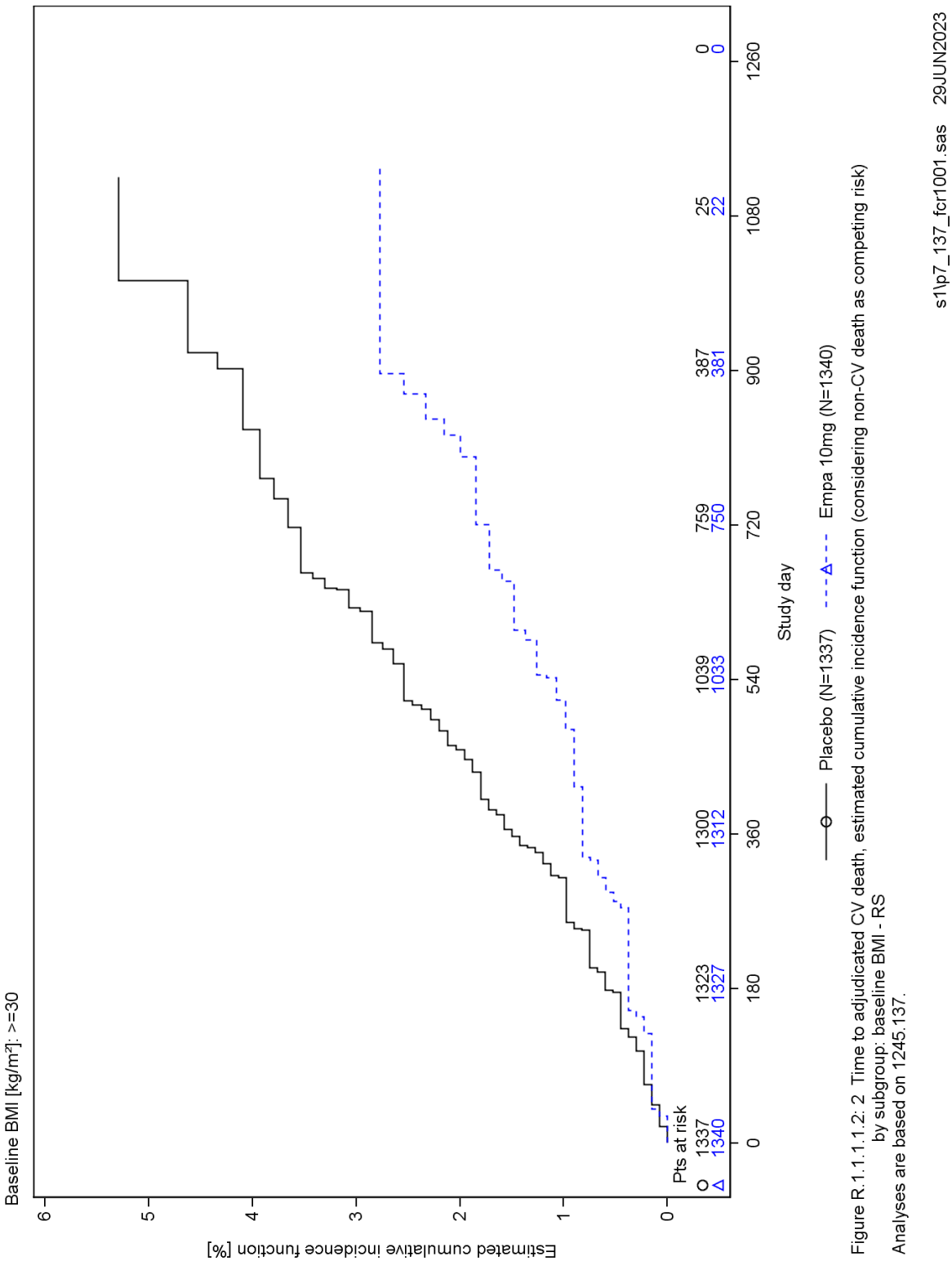


Figure R.1.1.1.1.2: 2 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) by subgroup: baseline BMI - RS

Analyses are based on 1245.137.

**Figure R.1.1.1.1.2: 3**

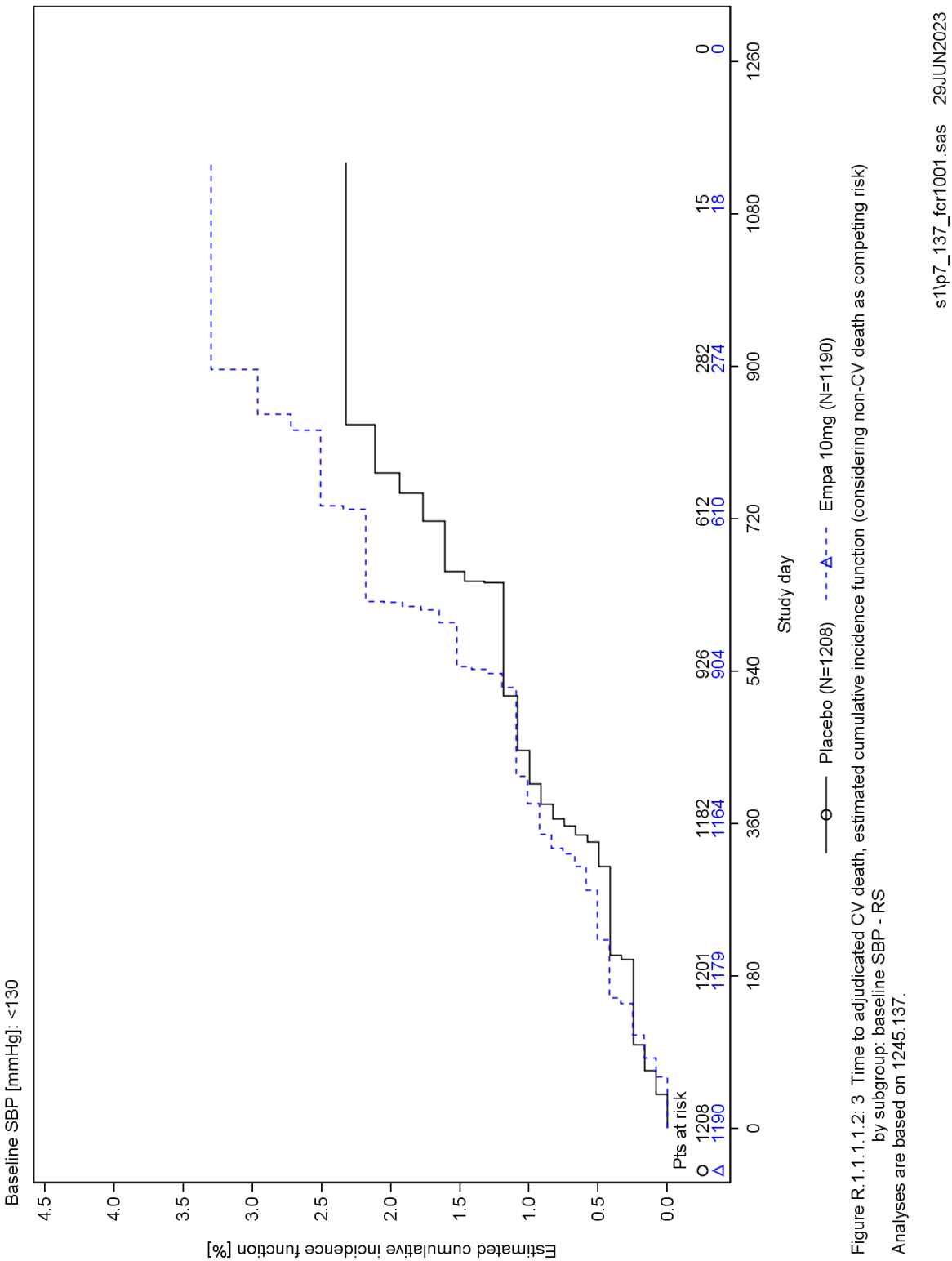


Figure R.1.1.1.1.2: 3 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on 1245.137.

**Figure R.1.1.1.1.2: 3**

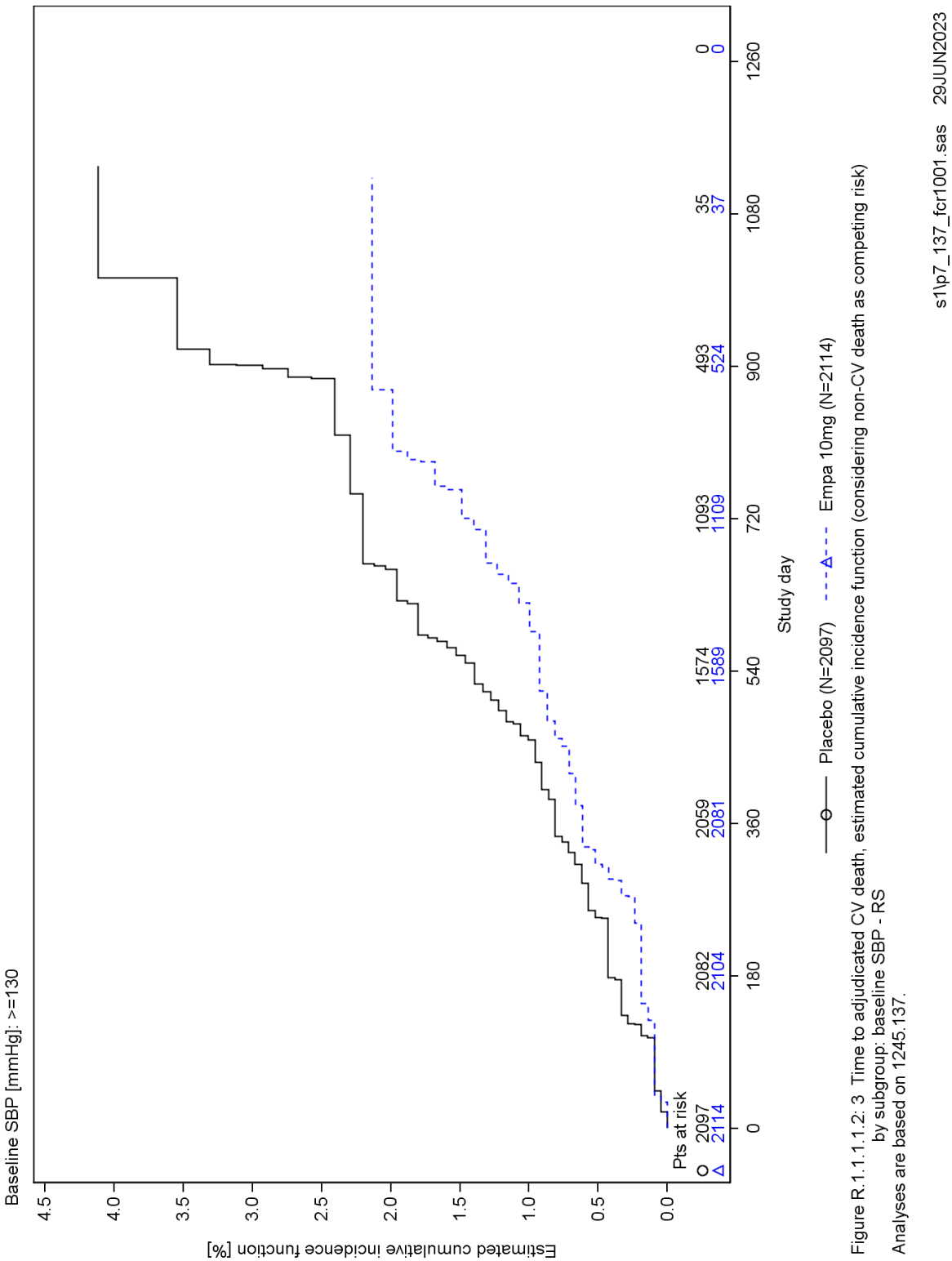


Figure R.1.1.1.1.2: 3 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on 1245.137.

**Figure R.1.1.1.1.2: 4**

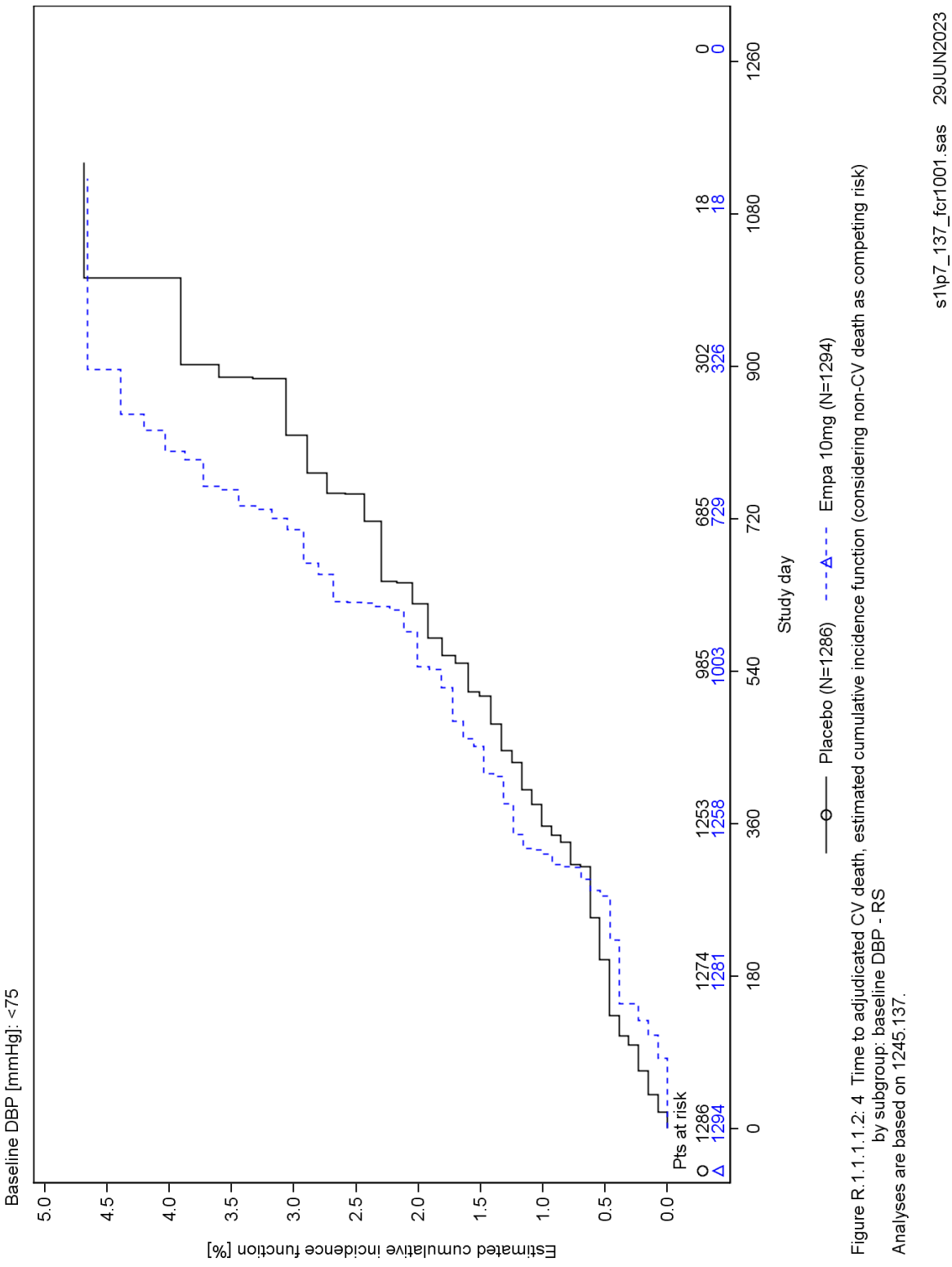


Figure R.1.1.1.1.2: 4 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk)
by subgroup: baseline DBP - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.1.2: 4**

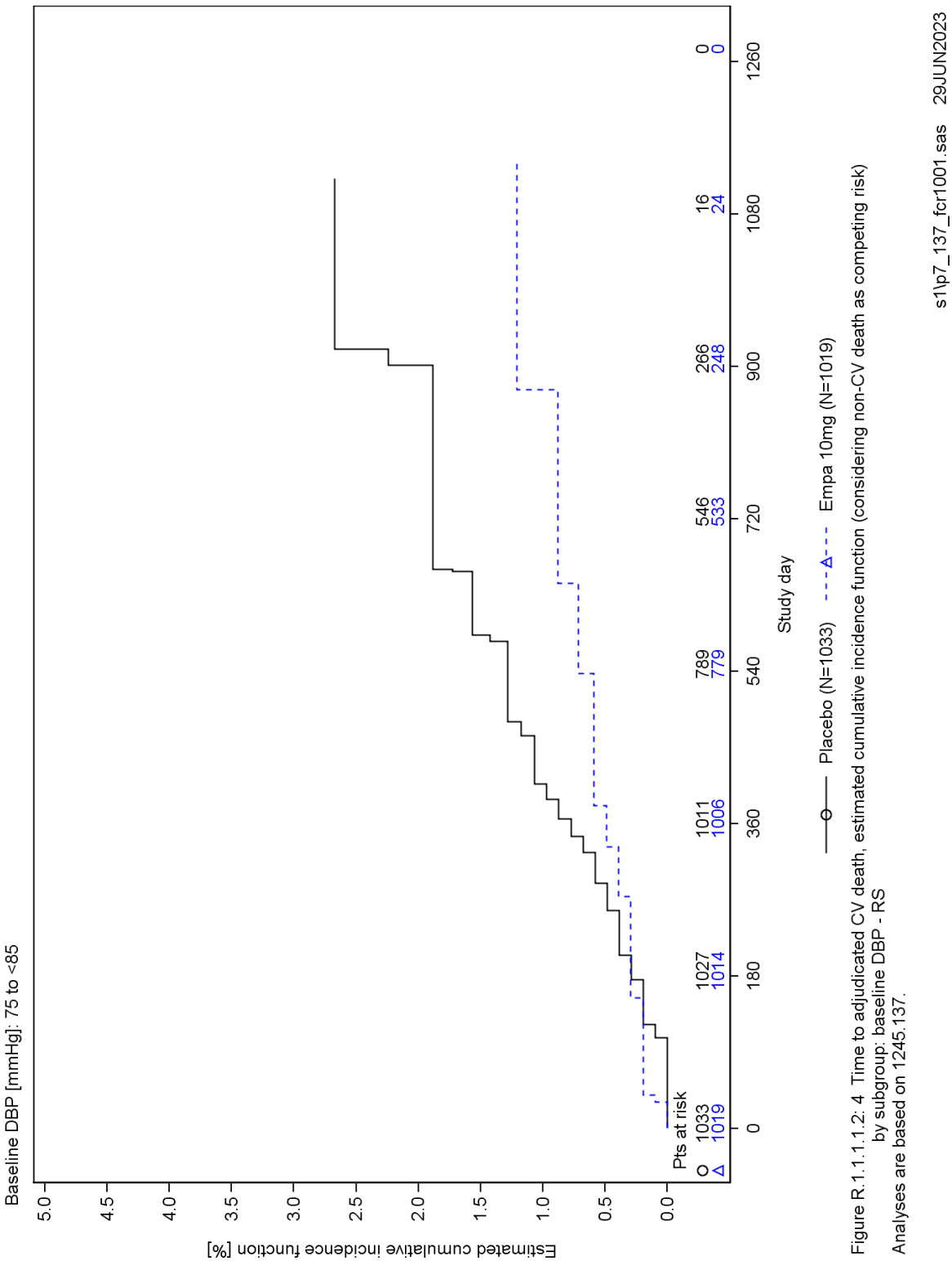


Figure R.1.1.1.1.2: 4 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk)
by subgroup: baseline DBP - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.1.2: 4**

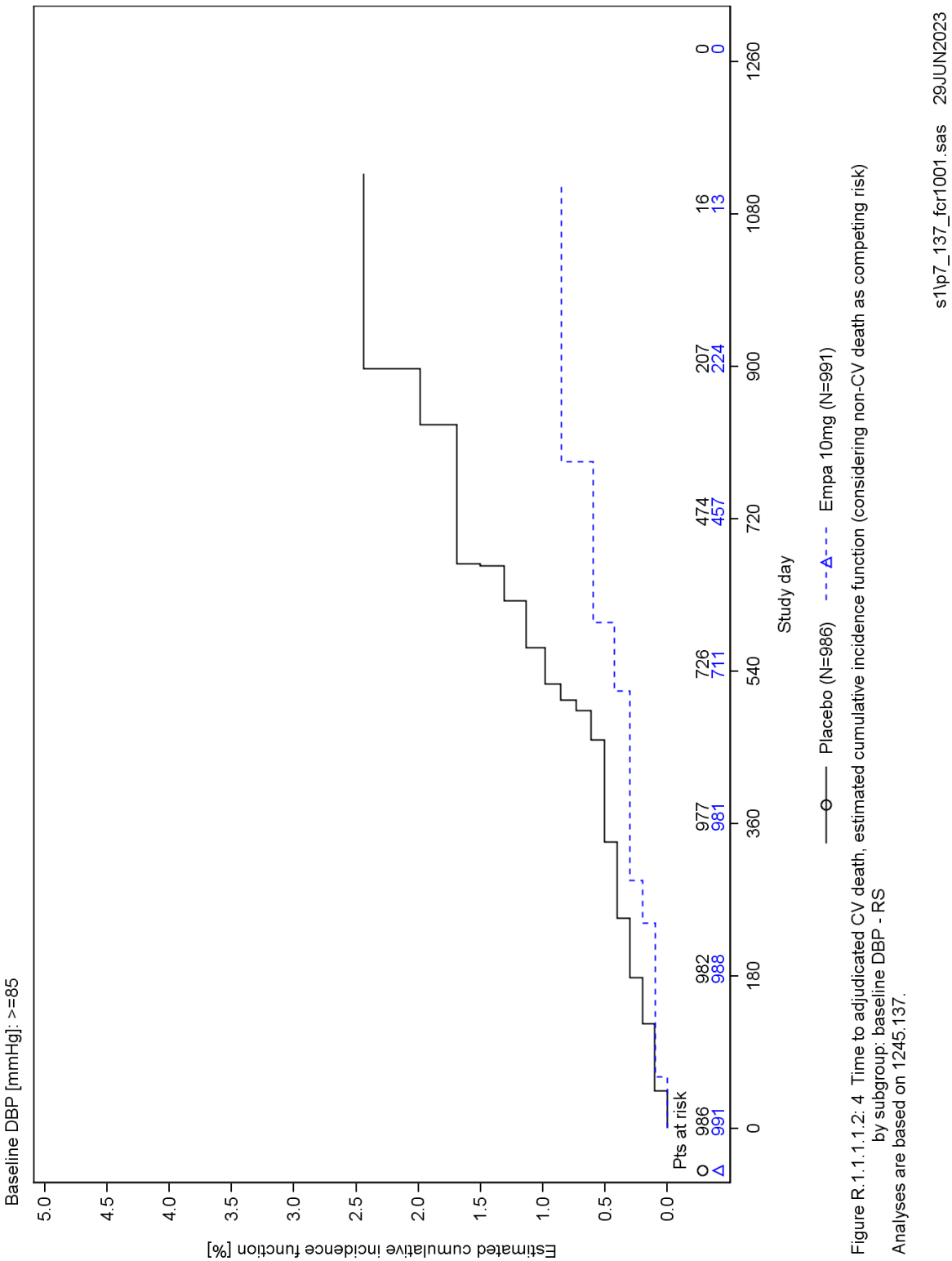


Figure R.1.1.1.1.2: 4 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) by subgroup: baseline DBP - RS

Analyses are based on 1245.137.

**R.1.1.1.1.3**

R.1.1.1.1.3 Time to adjudicated renal death

Table R.1.1.1.1.3: 1 Cox Regression for time to adjudicated renal death overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 4 | 0.1 | 0.06 | 3304 | 4 | 0.1 | 0.06 | 0.90 | (0.22,3.66) | 0.8837 | |
| Sex | | | | | | | | | | | | |
| Male | 2210 | 4 | 0.2 | 0.09 | 2207 | 3 | 0.1 | 0.07 | | | | |
| Female | 1095 | 0 | 0 | 0.00 | 1097 | 1 | 0.1 | 0.05 | | | | |
| Age [years] | | | | | | | | | | | | |
| <65 | 1501 | 2 | 0.1 | 0.07 | 1501 | 0 | 0 | 0.00 | | | | |
| >=65 | 1804 | 2 | 0.1 | 0.06 | 1803 | 4 | 0.2 | 0.11 | | | | |
| Region | | | | | | | | | | | | |
| North America | 873 | 1 | 0.1 | 0.06 | 844 | 1 | 0.1 | 0.06 | | | | |
| Europe | 1304 | 1 | 0.1 | 0.04 | 1344 | 1 | 0.1 | 0.04 | | | | |
| Japan | 308 | 0 | 0 | 0.00 | 304 | 0 | 0 | 0.00 | | | | |
| Other Asia | 820 | 2 | 0.2 | 0.13 | 812 | 2 | 0.2 | 0.13 | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | |
| Diabetic | 1515 | 2 | 0.1 | 0.07 | 1525 | 4 | 0.3 | 0.13 | | | | |
| Non-diabetic | 1790 | 2 | 0.1 | 0.06 | 1779 | 0 | 0 | 0.00 | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | |
| <30 | 1961 | 4 | 0.2 | 0.11 | 1955 | 1 | 0.1 | 0.03 | | | | |
| >=30 | 1337 | 0 | 0 | 0.00 | 1340 | 3 | 0.2 | 0.11 | | | | |
| Prior CV disease | | | | | | | | | | | | |
| No | 2401 | 2 | 0.1 | 0.04 | 2443 | 3 | 0.1 | 0.06 | | | | |
| Yes | 904 | 2 | 0.2 | 0.11 | 861 | 1 | 0.1 | 0.06 | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 1208 | 1 | 0.1 | 0.04 | 1190 | 1 | 0.1 | 0.04 | | | | |
| >=130 | 2097 | 3 | 0.1 | 0.07 | 2114 | 3 | 0.1 | 0.07 | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 1286 | 3 | 0.2 | 0.12 | 1294 | 1 | 0.1 | 0.04 | | | | |
| 75 to <85 | 1033 | 0 | 0 | 0.00 | 1019 | 1 | 0.1 | 0.05 | | | | |
| >=85 | 986 | 1 | 0.1 | 0.05 | 991 | 2 | 0.2 | 0.11 | | | | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.1.3: 1 Cox Regression for time to adjudicated renal death overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| History of heart failure | | | | | | | | | | | | |
| No | 2970 | 3 | 0.1 | 0.05 | 2979 | 4 | 0.1 | 0.07 | | | | |
| Yes | 334 | 1 | 0.3 | 0.15 | 324 | 0 | 0 | 0.00 | | | | |
| History of renal disease | | | | | | | | | | | | |
| Diabetic kidney disease | 1025 | 1 | 0.1 | 0.05 | 1032 | 4 | 0.4 | 0.19 | | | | |
| Glomerular disease | 816 | 1 | 0.1 | 0.06 | 853 | 0 | 0 | 0.00 | | | | |
| Hypertensive/renovascular disease | 739 | 0 | 0 | 0.00 | 706 | 0 | 0 | 0.00 | | | | |
| Other/Unknown | 725 | 2 | 0.3 | 0.14 | 713 | 0 | 0 | 0.00 | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 1151 | 2 | 0.2 | 0.09 | 1131 | 2 | 0.2 | 0.09 | | | | |
| 30 to <45 | 1461 | 2 | 0.1 | 0.07 | 1467 | 2 | 0.1 | 0.07 | | | | |
| >=45 | 693 | 0 | 0 | 0.00 | 706 | 0 | 0 | 0.00 | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 663 | 1 | 0.2 | 0.08 | 665 | 0 | 0 | 0.00 | | | | |
| Microalbuminuria (30 to <=300) | 937 | 1 | 0.1 | 0.05 | 927 | 1 | 0.1 | 0.05 | | | | |
| Macroalbuminuria (>300) | 1705 | 2 | 0.1 | 0.06 | 1712 | 3 | 0.2 | 0.09 | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | |
| Low, moderate or high | 833 | 0 | 0 | 0.00 | 839 | 0 | 0 | 0.00 | | | | |
| Very high | 2472 | 4 | 0.2 | 0.08 | 2465 | 4 | 0.2 | 0.08 | | | | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | |
| No | 508 | 1 | 0.2 | 0.11 | 473 | 1 | 0.2 | 0.11 | | | | |
| Yes | 2797 | 3 | 0.1 | 0.05 | 2831 | 3 | 0.1 | 0.05 | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | | |
| No | 1940 | 1 | 0.1 | 0.03 | 1908 | 1 | 0.1 | 0.03 | | | | |
| Yes | 1365 | 3 | 0.2 | 0.11 | 1396 | 3 | 0.2 | 0.11 | | | | |
| Baseline use of diuretics | | | | | | | | | | | | |
| No | 1852 | 1 | 0.1 | 0.03 | 1942 | 2 | 0.1 | 0.05 | | | | |
| Yes | 1453 | 3 | 0.2 | 0.10 | 1362 | 2 | 0.1 | 0.07 | | | | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.1.3: 1**

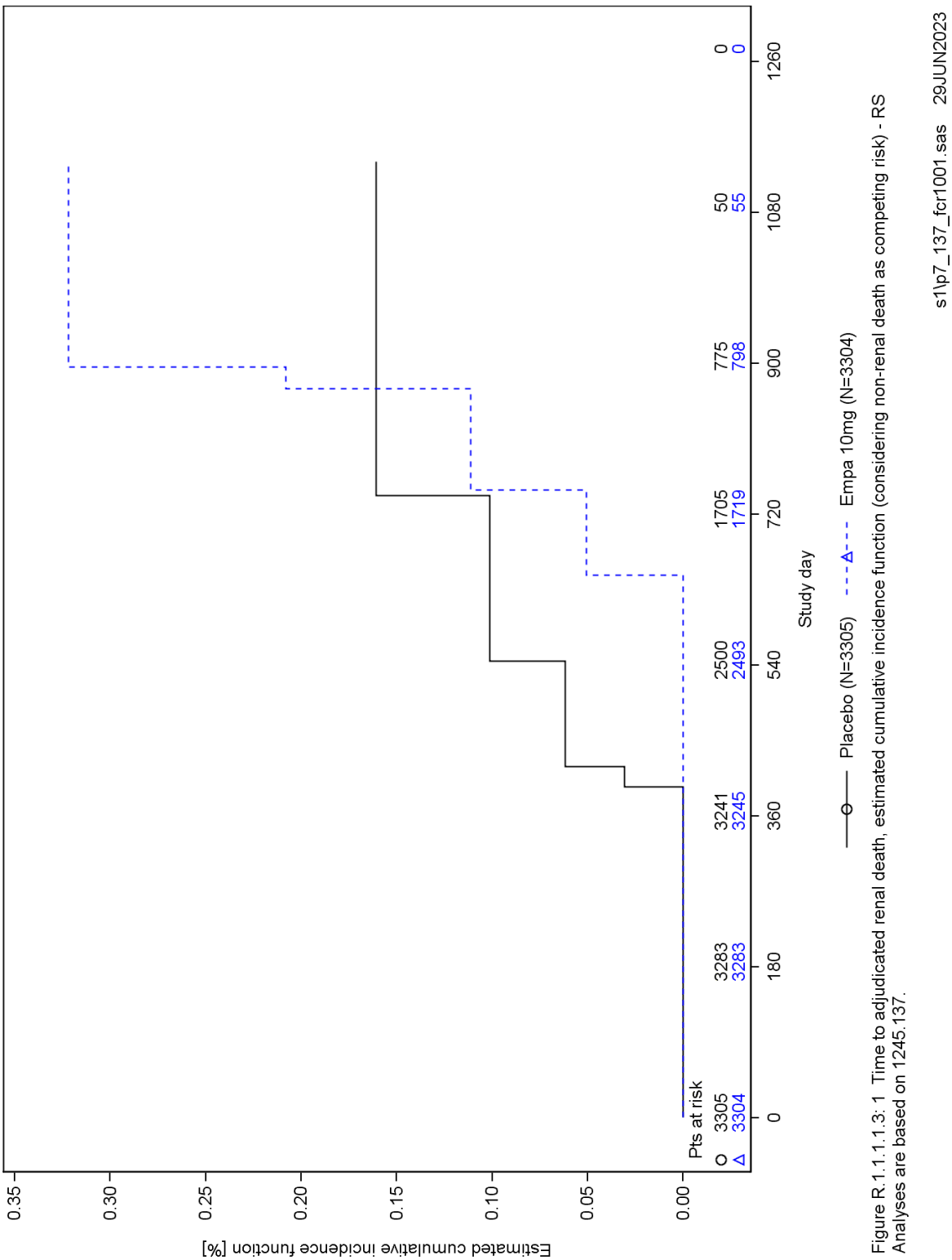


Figure R.1.1.1.1.3: 1 Time to adjudicated renal death, estimated cumulative incidence function (considering non-renal death as competing risk) - RS
Analyses are based on 1245.137.

**R.1.1.1.2**

R.1.1.1.2 Renal endpoints

R.1.1.1.2.1 Time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death

Table R.1.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 558 | 16.9 | 8.96 | 3304 | 432 | 13.1 | 6.85 | 0.72 | (0.64,0.82) | <0.0001 | |
| Sex | | | | | | | | | | | | 0.3620 |
| Male | 2210 | 394 | 17.8 | 9.48 | 2207 | 307 | 13.9 | 7.31 | 0.75 | (0.65,0.87) | 0.0002 | |
| Female | 1095 | 164 | 15.0 | 7.92 | 1097 | 125 | 11.4 | 5.94 | 0.66 | (0.52,0.83) | 0.0005 | |
| Age [years] | | | | | | | | | | | | 0.5392 |
| <65 | 1501 | 288 | 19.2 | 10.41 | 1501 | 231 | 15.4 | 8.25 | 0.75 | (0.63,0.89) | 0.0011 | |
| >=65 | 1804 | 270 | 15.0 | 7.80 | 1803 | 201 | 11.1 | 5.74 | 0.69 | (0.58,0.83) | <0.0001 | |
| Region | | | | | | | | | | | | 0.0616 |
| North America | 873 | 133 | 15.2 | 8.46 | 844 | 87 | 10.3 | 5.54 | 0.67 | (0.51,0.87) | 0.0032 | |
| Europe | 1304 | 190 | 14.6 | 7.25 | 1344 | 188 | 14.0 | 7.00 | 0.88 | (0.72,1.08) | 0.2113 | |
| Japan | 308 | 64 | 20.8 | 10.41 | 304 | 33 | 10.9 | 5.37 | 0.50 | (0.33,0.76) | 0.0011 | |
| Other Asia | 820 | 171 | 20.9 | 12.04 | 812 | 124 | 15.3 | 8.66 | 0.67 | (0.53,0.85) | 0.0008 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.0598 |
| Diabetic | 1515 | 306 | 20.2 | 10.54 | 1525 | 218 | 14.3 | 7.35 | 0.64 | (0.54,0.77) | <0.0001 | |
| Non-diabetic | 1790 | 252 | 14.1 | 7.58 | 1779 | 214 | 12.0 | 6.42 | 0.82 | (0.68,0.99) | 0.0350 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.4816 |
| <30 | 1961 | 319 | 16.3 | 8.83 | 1955 | 266 | 13.6 | 7.24 | 0.75 | (0.64,0.88) | 0.0006 | |
| >=30 | 1337 | 237 | 17.7 | 9.10 | 1340 | 165 | 12.3 | 6.31 | 0.68 | (0.56,0.83) | 0.0002 | |
| Prior CV disease | | | | | | | | | | | | 0.9928 |
| No | 2401 | 388 | 16.2 | 8.58 | 2443 | 310 | 12.7 | 6.68 | 0.73 | (0.63,0.85) | <0.0001 | |
| Yes | 904 | 170 | 18.8 | 9.96 | 861 | 122 | 14.2 | 7.35 | 0.73 | (0.58,0.92) | 0.0075 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1269 |
| <130 | 1208 | 145 | 12.0 | 6.25 | 1190 | 127 | 10.7 | 5.55 | 0.85 | (0.67,1.08) | 0.1764 | |
| >=130 | 2097 | 413 | 19.7 | 10.57 | 2114 | 305 | 14.4 | 7.60 | 0.68 | (0.59,0.79) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=40% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7009 |
| <75 | 1286 | 197 | 15.3 | 8.03 | 1294 | 162 | 12.5 | 6.40 | 0.72 | (0.58,0.89) | 0.0019 | |
| 75 to <85 | 1033 | 172 | 16.7 | 8.70 | 1019 | 134 | 13.2 | 6.86 | 0.78 | (0.62,0.98) | 0.0305 | |
| >=85 | 986 | 189 | 19.2 | 10.51 | 991 | 136 | 13.7 | 7.47 | 0.68 | (0.55,0.85) | 0.0006 | |
| History of heart failure | | | | | | | | | | | | 0.0971 |
| No | 2970 | 508 | 17.1 | 9.09 | 2979 | 382 | 12.8 | 6.72 | 0.70 | (0.61,0.80) | <0.0001 | |
| Yes | 334 | 50 | 15.0 | 7.81 | 324 | 50 | 15.4 | 8.17 | 1.00 | (0.67,1.47) | 0.9821 | |
| History of renal disease | | | | | | | | | | | | 0.5578 |
| Diabetic kidney disease | 1025 | 223 | 21.8 | 11.41 | 1032 | 161 | 15.6 | 8.10 | 0.65 | (0.53,0.80) | <0.0001 | |
| Glomerular disease | 816 | 142 | 17.4 | 9.66 | 853 | 117 | 13.7 | 7.48 | 0.77 | (0.60,0.98) | 0.0336 | |
| Hypertensive/renovascular disease | 739 | 96 | 13.0 | 6.92 | 706 | 82 | 11.6 | 5.95 | 0.82 | (0.61,1.11) | 0.1997 | |
| Other/Unknown | 725 | 97 | 13.4 | 6.84 | 713 | 72 | 10.1 | 5.24 | 0.73 | (0.54,1.00) | 0.0467 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6569 |
| <30 | 1151 | 317 | 27.5 | 15.08 | 1131 | 247 | 21.8 | 11.69 | 0.73 | (0.62,0.86) | 0.0002 | |
| 30 to <45 | 1461 | 175 | 12.0 | 6.19 | 1467 | 140 | 9.5 | 4.92 | 0.78 | (0.62,0.97) | 0.0287 | |
| >=45 | 693 | 66 | 9.5 | 5.08 | 706 | 45 | 6.4 | 3.35 | 0.64 | (0.44,0.93) | 0.0194 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0812 |
| Normal (<30) | 663 | 42 | 6.3 | 3.18 | 665 | 42 | 6.3 | 3.22 | 1.01 | (0.66,1.55) | 0.9688 | |
| Microalbuminuria (30 to <=300) | 937 | 78 | 8.3 | 4.26 | 927 | 67 | 7.2 | 3.69 | 0.91 | (0.65,1.26) | 0.5522 | |
| Macroalbuminuria (>300) | 1705 | 438 | 25.7 | 14.22 | 1712 | 323 | 18.9 | 10.14 | 0.67 | (0.58,0.78) | <0.0001 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0739 |
| Low, moderate or high | 833 | 41 | 4.9 | 2.52 | 839 | 44 | 5.2 | 2.73 | 1.09 | (0.71,1.67) | 0.6976 | |
| Very high | 2472 | 517 | 20.9 | 11.23 | 2465 | 388 | 15.7 | 8.28 | 0.72 | (0.64,0.83) | <0.0001 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.5159 |
| No | 508 | 98 | 19.3 | 10.85 | 473 | 81 | 17.1 | 9.49 | 0.79 | (0.59,1.06) | 0.1205 | |
| Yes | 2797 | 460 | 16.4 | 8.64 | 2831 | 351 | 12.4 | 6.44 | 0.71 | (0.62,0.82) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=40% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of beta-blockers | | | | | | | | | | | | 0.8545 |
| No | 1940 | 304 | 15.7 | 8.39 | 1908 | 228 | 11.9 | 6.32 | 0.72 | (0.60,0.85) | 0.0001 | |
| Yes | 1365 | 254 | 18.6 | 9.75 | 1396 | 204 | 14.6 | 7.57 | 0.73 | (0.61,0.88) | 0.0010 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9333 |
| No | 1852 | 293 | 15.8 | 8.53 | 1942 | 233 | 12.0 | 6.40 | 0.73 | (0.61,0.87) | 0.0003 | |
| Yes | 1453 | 265 | 18.2 | 9.48 | 1362 | 199 | 14.6 | 7.48 | 0.72 | (0.60,0.87) | 0.0005 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=40% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.2.1: 1**

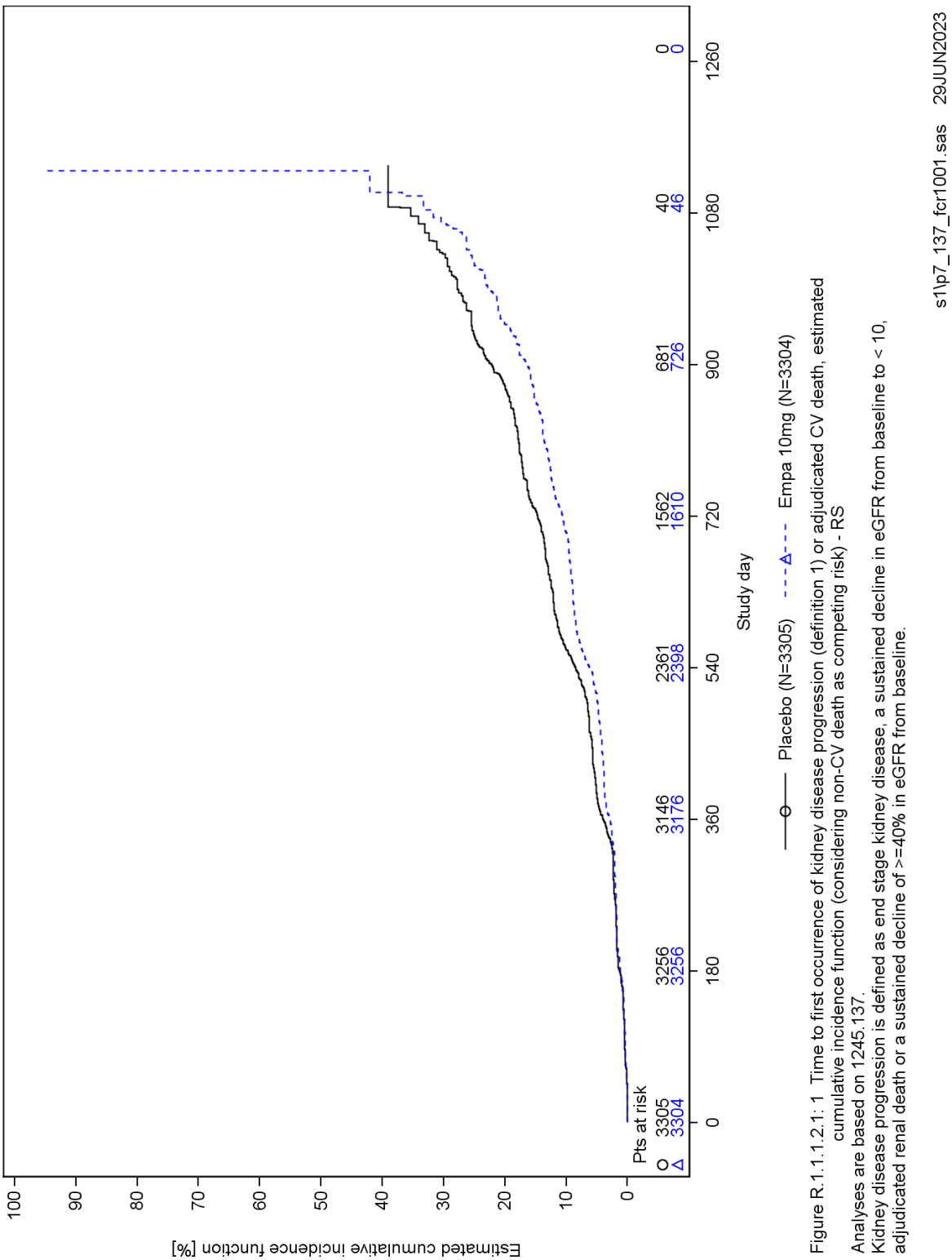


Figure R.1.1.1.2.1: 1 Time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=40% in eGFR from baseline.

R.1.1.1.2.2 Time to first occurrence of kidney disease progression (definition 1)

Table R.1.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 504 | 15.2 | 8.09 | 3304 | 384 | 11.6 | 6.09 | 0.71 | (0.62,0.81) | <0.0001 | |
| Sex | | | | | | | | | | | | 0.4469 |
| Male | 2210 | 359 | 16.2 | 8.63 | 2207 | 273 | 12.4 | 6.50 | 0.73 | (0.63,0.86) | 0.0001 | |
| Female | 1095 | 145 | 13.2 | 7.00 | 1097 | 111 | 10.1 | 5.27 | 0.65 | (0.51,0.84) | 0.0008 | |
| Age [years] | | | | | | | | | | | | 0.4829 |
| <65 | 1501 | 281 | 18.7 | 10.16 | 1501 | 222 | 14.8 | 7.93 | 0.73 | (0.62,0.88) | 0.0006 | |
| >=65 | 1804 | 223 | 12.4 | 6.44 | 1803 | 162 | 9.0 | 4.62 | 0.67 | (0.54,0.82) | <0.0001 | |
| Region | | | | | | | | | | | | 0.0635 |
| North America | 873 | 111 | 12.7 | 7.06 | 844 | 71 | 8.4 | 4.52 | 0.66 | (0.49,0.88) | 0.0056 | |
| Europe | 1304 | 165 | 12.7 | 6.29 | 1344 | 163 | 12.1 | 6.07 | 0.87 | (0.70,1.08) | 0.1937 | |
| Japan | 308 | 63 | 20.5 | 10.25 | 304 | 31 | 10.2 | 5.04 | 0.47 | (0.30,0.72) | 0.0006 | |
| Other Asia | 820 | 165 | 20.1 | 11.62 | 812 | 119 | 14.7 | 8.31 | 0.67 | (0.53,0.85) | 0.0009 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.0713 |
| Diabetic | 1515 | 260 | 17.2 | 8.95 | 1525 | 182 | 11.9 | 6.13 | 0.63 | (0.52,0.76) | <0.0001 | |
| Non-diabetic | 1790 | 244 | 13.6 | 7.34 | 1779 | 202 | 11.4 | 6.06 | 0.80 | (0.66,0.96) | 0.0191 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.8534 |
| <30 | 1961 | 304 | 15.5 | 8.42 | 1955 | 239 | 12.2 | 6.51 | 0.70 | (0.59,0.83) | <0.0001 | |
| >=30 | 1337 | 198 | 14.8 | 7.60 | 1340 | 145 | 10.8 | 5.55 | 0.72 | (0.58,0.89) | 0.0026 | |
| Prior CV disease | | | | | | | | | | | | 0.9006 |
| No | 2401 | 367 | 15.3 | 8.12 | 2443 | 289 | 11.8 | 6.22 | 0.71 | (0.61,0.83) | <0.0001 | |
| Yes | 904 | 137 | 15.2 | 8.03 | 861 | 95 | 11.0 | 5.72 | 0.70 | (0.54,0.91) | 0.0080 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3845 |
| <130 | 1208 | 130 | 10.8 | 5.60 | 1190 | 106 | 8.9 | 4.63 | 0.78 | (0.60,1.01) | 0.0606 | |
| >=130 | 2097 | 374 | 17.8 | 9.57 | 2114 | 278 | 13.2 | 6.92 | 0.68 | (0.59,0.80) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=40% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3100 |
| <75 | 1286 | 173 | 13.5 | 7.05 | 1294 | 126 | 9.7 | 4.98 | 0.63 | (0.50,0.79) | <0.0001 | |
| 75 to <85 | 1033 | 156 | 15.1 | 7.89 | 1019 | 127 | 12.5 | 6.50 | 0.81 | (0.64,1.02) | 0.0780 | |
| >=85 | 986 | 175 | 17.7 | 9.73 | 991 | 131 | 13.2 | 7.20 | 0.71 | (0.56,0.89) | 0.0030 | |
| History of heart failure | | | | | | | | | | | | 0.4311 |
| No | 2970 | 465 | 15.7 | 8.32 | 2979 | 351 | 11.8 | 6.17 | 0.70 | (0.61,0.80) | <0.0001 | |
| Yes | 334 | 39 | 11.7 | 6.09 | 324 | 33 | 10.2 | 5.39 | 0.85 | (0.53,1.35) | 0.4931 | |
| History of renal disease | | | | | | | | | | | | 0.6172 |
| Diabetic kidney disease | 1025 | 189 | 18.4 | 9.67 | 1032 | 137 | 13.3 | 6.89 | 0.64 | (0.52,0.80) | <0.0001 | |
| Glomerular disease | 816 | 139 | 17.0 | 9.46 | 853 | 115 | 13.5 | 7.36 | 0.77 | (0.60,0.99) | 0.0419 | |
| Hypertensive/renovascular disease | 739 | 87 | 11.8 | 6.27 | 706 | 72 | 10.2 | 5.22 | 0.79 | (0.58,1.08) | 0.1354 | |
| Other/Unknown | 725 | 89 | 12.3 | 6.28 | 713 | 60 | 8.4 | 4.37 | 0.67 | (0.48,0.92) | 0.0147 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.5269 |
| <30 | 1151 | 292 | 25.4 | 13.89 | 1131 | 225 | 19.9 | 10.65 | 0.72 | (0.60,0.85) | 0.0002 | |
| 30 to <45 | 1461 | 148 | 10.1 | 5.23 | 1467 | 118 | 8.0 | 4.14 | 0.78 | (0.61,0.99) | 0.0394 | |
| >=45 | 693 | 64 | 9.2 | 4.93 | 706 | 41 | 5.8 | 3.06 | 0.59 | (0.40,0.88) | 0.0093 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.1426 |
| Normal (<30) | 663 | 31 | 4.7 | 2.35 | 665 | 30 | 4.5 | 2.30 | 0.97 | (0.59,1.60) | 0.9089 | |
| Microalbuminuria (30 to <=300) | 937 | 55 | 5.9 | 3.00 | 927 | 48 | 5.2 | 2.65 | 0.93 | (0.63,1.37) | 0.7002 | |
| Macroalbuminuria (>300) | 1705 | 418 | 24.5 | 13.57 | 1712 | 306 | 17.9 | 9.61 | 0.67 | (0.58,0.78) | <0.0001 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2404 |
| Low, moderate or high | 833 | 38 | 4.6 | 2.34 | 839 | 36 | 4.3 | 2.23 | 0.96 | (0.61,1.51) | 0.8567 | |
| Very high | 2472 | 466 | 18.9 | 10.12 | 2465 | 348 | 14.1 | 7.42 | 0.72 | (0.63,0.83) | <0.0001 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.3664 |
| No | 508 | 85 | 16.7 | 9.41 | 473 | 73 | 15.4 | 8.55 | 0.81 | (0.59,1.11) | 0.1820 | |
| Yes | 2797 | 419 | 15.0 | 7.87 | 2831 | 311 | 11.0 | 5.71 | 0.69 | (0.59,0.80) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=40% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6780 |
| No | 1940 | 288 | 14.8 | 7.94 | 1908 | 210 | 11.0 | 5.82 | 0.69 | (0.58,0.83) | <0.0001 | |
| Yes | 1365 | 216 | 15.8 | 8.29 | 1396 | 174 | 12.5 | 6.45 | 0.73 | (0.60,0.89) | 0.0022 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.8871 |
| No | 1852 | 278 | 15.0 | 8.09 | 1942 | 217 | 11.2 | 5.96 | 0.72 | (0.60,0.86) | 0.0002 | |
| Yes | 1453 | 226 | 15.6 | 8.09 | 1362 | 167 | 12.3 | 6.28 | 0.70 | (0.57,0.86) | 0.0006 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=40% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.2.2: 1**

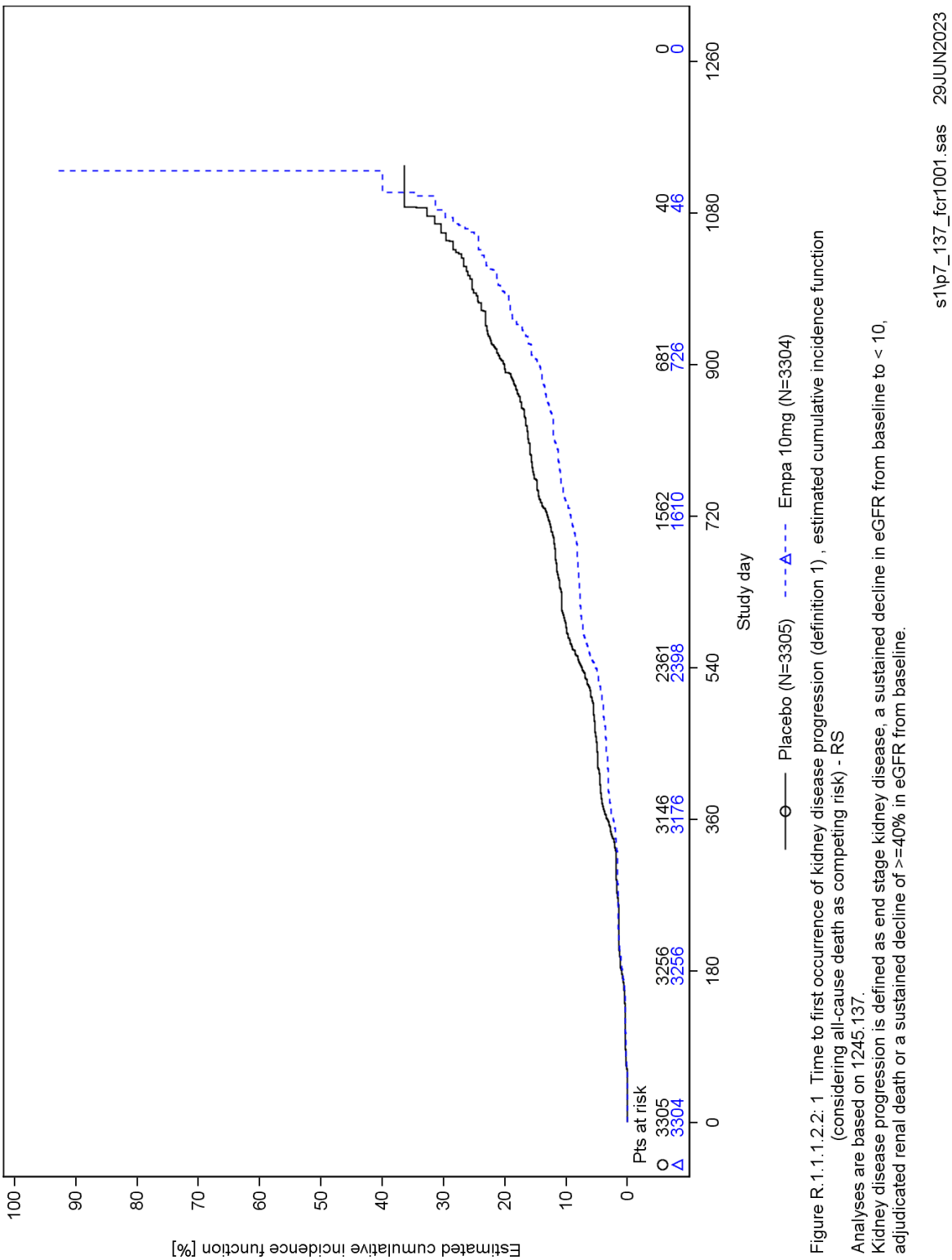


Figure R.1.1.1.2.2: 1 Time to first occurrence of kidney disease progression (definition 1) , estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=40% in eGFR from baseline.

R.1.1.1.2.3 Time to first occurrence of kidney disease progression (definition 2)

Table R.1.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 332 | 10.0 | 5.25 | 3304 | 227 | 6.9 | 3.56 | 0.64 | (0.54,0.76) | <0.0001 | |
| Sex | | | | | | | | | | | | 0.4130 |
| Male | 2210 | 238 | 10.8 | 5.64 | 2207 | 164 | 7.4 | 3.86 | 0.67 | (0.55,0.82) | <0.0001 | |
| Female | 1095 | 94 | 8.6 | 4.47 | 1097 | 63 | 5.7 | 2.97 | 0.57 | (0.42,0.79) | 0.0007 | |
| Age [years] | | | | | | | | | | | | 0.6037 |
| <65 | 1501 | 200 | 13.3 | 7.11 | 1501 | 142 | 9.5 | 5.00 | 0.66 | (0.53,0.82) | 0.0002 | |
| >=65 | 1804 | 132 | 7.3 | 3.76 | 1803 | 85 | 4.7 | 2.40 | 0.60 | (0.46,0.79) | 0.0003 | |
| Region | | | | | | | | | | | | 0.2861 |
| North America | 873 | 73 | 8.4 | 4.58 | 844 | 36 | 4.3 | 2.27 | 0.53 | (0.35,0.78) | 0.0016 | |
| Europe | 1304 | 104 | 8.0 | 3.92 | 1344 | 90 | 6.7 | 3.31 | 0.75 | (0.56,0.99) | 0.0426 | |
| Japan | 308 | 42 | 13.6 | 6.68 | 304 | 19 | 6.3 | 3.07 | 0.45 | (0.26,0.78) | 0.0043 | |
| Other Asia | 820 | 113 | 13.8 | 7.83 | 812 | 82 | 10.1 | 5.65 | 0.68 | (0.51,0.90) | 0.0079 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.0885 |
| Diabetic | 1515 | 175 | 11.6 | 5.93 | 1525 | 108 | 7.1 | 3.59 | 0.55 | (0.44,0.71) | <0.0001 | |
| Non-diabetic | 1790 | 157 | 8.8 | 4.66 | 1779 | 119 | 6.7 | 3.54 | 0.74 | (0.59,0.95) | 0.0154 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.8208 |
| <30 | 1961 | 205 | 10.5 | 5.59 | 1955 | 149 | 7.6 | 4.01 | 0.65 | (0.52,0.80) | <0.0001 | |
| >=30 | 1337 | 126 | 9.4 | 4.77 | 1340 | 78 | 5.8 | 2.95 | 0.62 | (0.47,0.82) | 0.0010 | |
| Prior CV disease | | | | | | | | | | | | 0.3206 |
| No | 2401 | 244 | 10.2 | 5.32 | 2443 | 181 | 7.4 | 3.85 | 0.67 | (0.56,0.82) | <0.0001 | |
| Yes | 904 | 88 | 9.7 | 5.08 | 861 | 46 | 5.3 | 2.75 | 0.55 | (0.38,0.79) | 0.0010 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.2397 |
| <130 | 1208 | 73 | 6.0 | 3.12 | 1190 | 59 | 5.0 | 2.56 | 0.77 | (0.55,1.09) | 0.1381 | |
| >=130 | 2097 | 259 | 12.4 | 6.51 | 2114 | 168 | 7.9 | 4.13 | 0.61 | (0.50,0.74) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=50% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | p-value |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.0679 |
| <75 | 1286 | 111 | 8.6 | 4.48 | 1294 | 64 | 4.9 | 2.51 | 0.50 | (0.36,0.68) | <0.0001 | |
| 75 to <85 | 1033 | 96 | 9.3 | 4.79 | 1019 | 78 | 7.7 | 3.95 | 0.83 | (0.61,1.12) | 0.2156 | |
| >=85 | 986 | 125 | 12.7 | 6.80 | 991 | 85 | 8.6 | 4.60 | 0.64 | (0.49,0.85) | 0.0018 | |
| History of heart failure | | | | | | | | | | | | 0.5495 |
| No | 2970 | 310 | 10.4 | 5.47 | 2979 | 210 | 7.0 | 3.65 | 0.63 | (0.53,0.76) | <0.0001 | |
| Yes | 334 | 22 | 6.6 | 3.38 | 324 | 17 | 5.2 | 2.74 | 0.78 | (0.41,1.46) | 0.4336 | |
| History of renal disease | | | | | | | | | | | | 0.7163 |
| Diabetic kidney disease | 1025 | 133 | 13.0 | 6.70 | 1032 | 85 | 8.2 | 4.20 | 0.56 | (0.43,0.74) | <0.0001 | |
| Glomerular disease | 816 | 95 | 11.6 | 6.37 | 853 | 69 | 8.1 | 4.37 | 0.68 | (0.50,0.93) | 0.0156 | |
| Hypertensive/renovascular disease | 739 | 52 | 7.0 | 3.70 | 706 | 37 | 5.2 | 2.66 | 0.69 | (0.45,1.05) | 0.0803 | |
| Other/Unknown | 725 | 52 | 7.2 | 3.62 | 713 | 36 | 5.0 | 2.60 | 0.72 | (0.47,1.10) | 0.1300 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4013 |
| <30 | 1151 | 211 | 18.3 | 9.83 | 1131 | 156 | 13.8 | 7.25 | 0.70 | (0.57,0.87) | 0.0009 | |
| 30 to <45 | 1461 | 87 | 6.0 | 3.04 | 1467 | 53 | 3.6 | 1.85 | 0.60 | (0.42,0.84) | 0.0029 | |
| >=45 | 693 | 34 | 4.9 | 2.60 | 706 | 18 | 2.5 | 1.33 | 0.48 | (0.27,0.86) | 0.0132 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2140 |
| Normal (<30) | 663 | 21 | 3.2 | 1.58 | 665 | 15 | 2.3 | 1.14 | 0.72 | (0.37,1.40) | 0.3322 | |
| Microalbuminuria (30 to <=300) | 937 | 24 | 2.6 | 1.31 | 927 | 23 | 2.5 | 1.26 | 1.04 | (0.58,1.84) | 0.9017 | |
| Macroalbuminuria (>300) | 1705 | 287 | 16.8 | 9.09 | 1712 | 189 | 11.0 | 5.83 | 0.61 | (0.51,0.73) | <0.0001 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5840 |
| Low, moderate or high | 833 | 19 | 2.3 | 1.16 | 839 | 15 | 1.8 | 0.92 | 0.80 | (0.41,1.57) | 0.5149 | |
| Very high | 2472 | 313 | 12.7 | 6.68 | 2465 | 212 | 8.6 | 4.46 | 0.66 | (0.55,0.78) | <0.0001 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.7551 |
| No | 508 | 65 | 12.8 | 7.13 | 473 | 49 | 10.4 | 5.64 | 0.67 | (0.46,0.98) | 0.0365 | |
| Yes | 2797 | 267 | 9.5 | 4.94 | 2831 | 178 | 6.3 | 3.23 | 0.63 | (0.52,0.76) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=50% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9431 |
| No | 1940 | 186 | 9.6 | 5.06 | 1908 | 126 | 6.6 | 3.45 | 0.65 | (0.51,0.81) | 0.0002 | |
| Yes | 1365 | 146 | 10.7 | 5.53 | 1396 | 101 | 7.2 | 3.70 | 0.64 | (0.49,0.82) | 0.0005 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2211 |
| No | 1852 | 176 | 9.5 | 5.05 | 1942 | 133 | 6.8 | 3.61 | 0.71 | (0.56,0.89) | 0.0025 | |
| Yes | 1453 | 156 | 10.7 | 5.50 | 1362 | 94 | 6.9 | 3.49 | 0.57 | (0.44,0.74) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=50% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.2.3: 1**

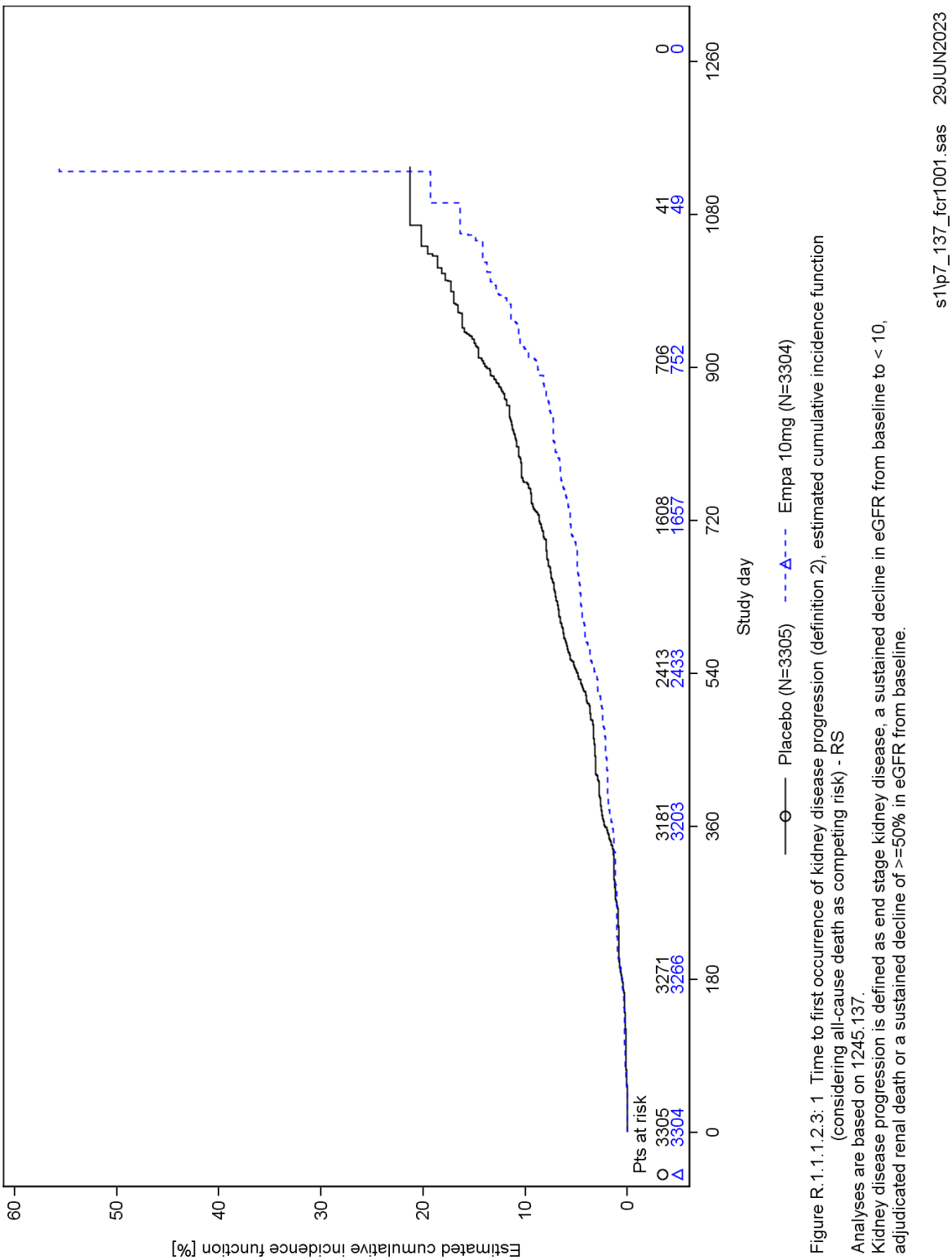


Figure R.1.1.1.2.3: 1 Time to first occurrence of kidney disease progression (definition 2), estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=50% in eGFR from baseline.

R.1.1.1.2.4

R.1.1.1.2.4 Time to first occurrence of kidney disease progression (definition 3)

Table R.1.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 273 | 8.3 | 4.31 | 3304 | 191 | 5.8 | 2.99 | 0.67 | (0.56,0.81) | <0.0001 | |
| Sex | | | | | | | | | | | | 0.4237 |
| Male | 2210 | 194 | 8.8 | 4.58 | 2207 | 137 | 6.2 | 3.22 | 0.70 | (0.56,0.87) | 0.0016 | |
| Female | 1095 | 79 | 7.2 | 3.75 | 1097 | 54 | 4.9 | 2.54 | 0.59 | (0.42,0.84) | 0.0032 | |
| Age [years] | | | | | | | | | | | | 0.4348 |
| <65 | 1501 | 163 | 10.9 | 5.77 | 1501 | 120 | 8.0 | 4.21 | 0.70 | (0.56,0.89) | 0.0035 | |
| >=65 | 1804 | 110 | 6.1 | 3.13 | 1803 | 71 | 3.9 | 2.00 | 0.60 | (0.45,0.82) | 0.0010 | |
| Region | | | | | | | | | | | | 0.5743 |
| North America | 873 | 64 | 7.3 | 4.00 | 844 | 33 | 3.9 | 2.08 | 0.57 | (0.37,0.87) | 0.0085 | |
| Europe | 1304 | 84 | 6.4 | 3.16 | 1344 | 75 | 5.6 | 2.75 | 0.77 | (0.56,1.05) | 0.0952 | |
| Japan | 308 | 30 | 9.7 | 4.74 | 304 | 15 | 4.9 | 2.42 | 0.52 | (0.28,0.96) | 0.0373 | |
| Other Asia | 820 | 95 | 11.6 | 6.54 | 812 | 68 | 8.4 | 4.67 | 0.68 | (0.50,0.94) | 0.0176 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1264 |
| Diabetic | 1515 | 145 | 9.6 | 4.90 | 1525 | 91 | 6.0 | 3.02 | 0.58 | (0.45,0.75) | <0.0001 | |
| Non-diabetic | 1790 | 128 | 7.2 | 3.79 | 1779 | 100 | 5.6 | 2.96 | 0.77 | (0.60,1.01) | 0.0558 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9524 |
| <30 | 1961 | 168 | 8.6 | 4.57 | 1955 | 124 | 6.3 | 3.33 | 0.67 | (0.53,0.84) | 0.0007 | |
| >=30 | 1337 | 104 | 7.8 | 3.93 | 1340 | 67 | 5.0 | 2.53 | 0.66 | (0.48,0.90) | 0.0080 | |
| Prior CV disease | | | | | | | | | | | | 0.1733 |
| No | 2401 | 199 | 8.3 | 4.32 | 2443 | 155 | 6.3 | 3.29 | 0.72 | (0.58,0.89) | 0.0022 | |
| Yes | 904 | 74 | 8.2 | 4.26 | 861 | 36 | 4.2 | 2.14 | 0.53 | (0.35,0.78) | 0.0016 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8086 |
| <130 | 1208 | 63 | 5.2 | 2.69 | 1190 | 46 | 3.9 | 1.99 | 0.70 | (0.48,1.02) | 0.0656 | |
| >=130 | 2097 | 210 | 10.0 | 5.25 | 2114 | 145 | 6.9 | 3.55 | 0.66 | (0.54,0.82) | 0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=57% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.1154 |
| <75 | 1286 | 90 | 7.0 | 3.62 | 1294 | 53 | 4.1 | 2.07 | 0.52 | (0.37,0.72) | 0.0001 | |
| 75 to <85 | 1033 | 83 | 8.0 | 4.13 | 1019 | 67 | 6.6 | 3.39 | 0.85 | (0.61,1.17) | 0.3176 | |
| >=85 | 986 | 100 | 10.1 | 5.42 | 991 | 71 | 7.2 | 3.83 | 0.68 | (0.50,0.92) | 0.0123 | |
| History of heart failure | | | | | | | | | | | | 0.5391 |
| No | 2970 | 256 | 8.6 | 4.50 | 2979 | 177 | 5.9 | 3.07 | 0.66 | (0.54,0.80) | <0.0001 | |
| Yes | 334 | 17 | 5.1 | 2.61 | 324 | 14 | 4.3 | 2.24 | 0.83 | (0.41,1.69) | 0.6079 | |
| History of renal disease | | | | | | | | | | | | 0.8006 |
| Diabetic kidney disease | 1025 | 111 | 10.8 | 5.56 | 1032 | 73 | 7.1 | 3.60 | 0.60 | (0.45,0.81) | 0.0009 | |
| Glomerular disease | 816 | 76 | 9.3 | 5.07 | 853 | 61 | 7.2 | 3.86 | 0.76 | (0.54,1.06) | 0.1057 | |
| Hypertensive/renovascular disease | 739 | 40 | 5.4 | 2.85 | 706 | 29 | 4.1 | 2.08 | 0.69 | (0.43,1.12) | 0.1325 | |
| Other/Unknown | 725 | 46 | 6.3 | 3.19 | 713 | 28 | 3.9 | 2.02 | 0.65 | (0.40,1.03) | 0.0683 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.9005 |
| <30 | 1151 | 189 | 16.4 | 8.76 | 1131 | 135 | 11.9 | 6.26 | 0.70 | (0.56,0.87) | 0.0014 | |
| 30 to <45 | 1461 | 64 | 4.4 | 2.23 | 1467 | 43 | 2.9 | 1.50 | 0.66 | (0.45,0.98) | 0.0379 | |
| >=45 | 693 | 20 | 2.9 | 1.53 | 706 | 13 | 1.8 | 0.96 | 0.59 | (0.29,1.19) | 0.1420 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2818 |
| Normal (<30) | 663 | 15 | 2.3 | 1.13 | 665 | 11 | 1.7 | 0.84 | 0.73 | (0.33,1.59) | 0.4246 | |
| Microalbuminuria (30 to <=300) | 937 | 20 | 2.1 | 1.09 | 927 | 20 | 2.2 | 1.10 | 1.08 | (0.58,2.00) | 0.8136 | |
| Macroalbuminuria (>300) | 1705 | 238 | 14.0 | 7.49 | 1712 | 160 | 9.3 | 4.92 | 0.64 | (0.52,0.78) | <0.0001 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.9683 |
| Low, moderate or high | 833 | 12 | 1.4 | 0.73 | 839 | 8 | 1.0 | 0.49 | 0.67 | (0.27,1.64) | 0.3840 | |
| Very high | 2472 | 261 | 10.6 | 5.55 | 2465 | 183 | 7.4 | 3.84 | 0.68 | (0.57,0.83) | <0.0001 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.9187 |
| No | 508 | 57 | 11.2 | 6.23 | 473 | 41 | 8.7 | 4.70 | 0.65 | (0.44,0.97) | 0.0369 | |
| Yes | 2797 | 216 | 7.7 | 3.98 | 2831 | 150 | 5.3 | 2.72 | 0.67 | (0.54,0.82) | 0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=57% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9962 |
| No | 1940 | 154 | 7.9 | 4.17 | 1908 | 107 | 5.6 | 2.93 | 0.67 | (0.52,0.86) | 0.0015 | |
| Yes | 1365 | 119 | 8.7 | 4.49 | 1396 | 84 | 6.0 | 3.08 | 0.67 | (0.50,0.88) | 0.0049 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.5309 |
| No | 1852 | 145 | 7.8 | 4.15 | 1942 | 109 | 5.6 | 2.95 | 0.71 | (0.55,0.91) | 0.0063 | |
| Yes | 1453 | 128 | 8.8 | 4.50 | 1362 | 82 | 6.0 | 3.04 | 0.63 | (0.47,0.83) | 0.0010 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=57% in eGFR from baseline.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.2.4: 1**

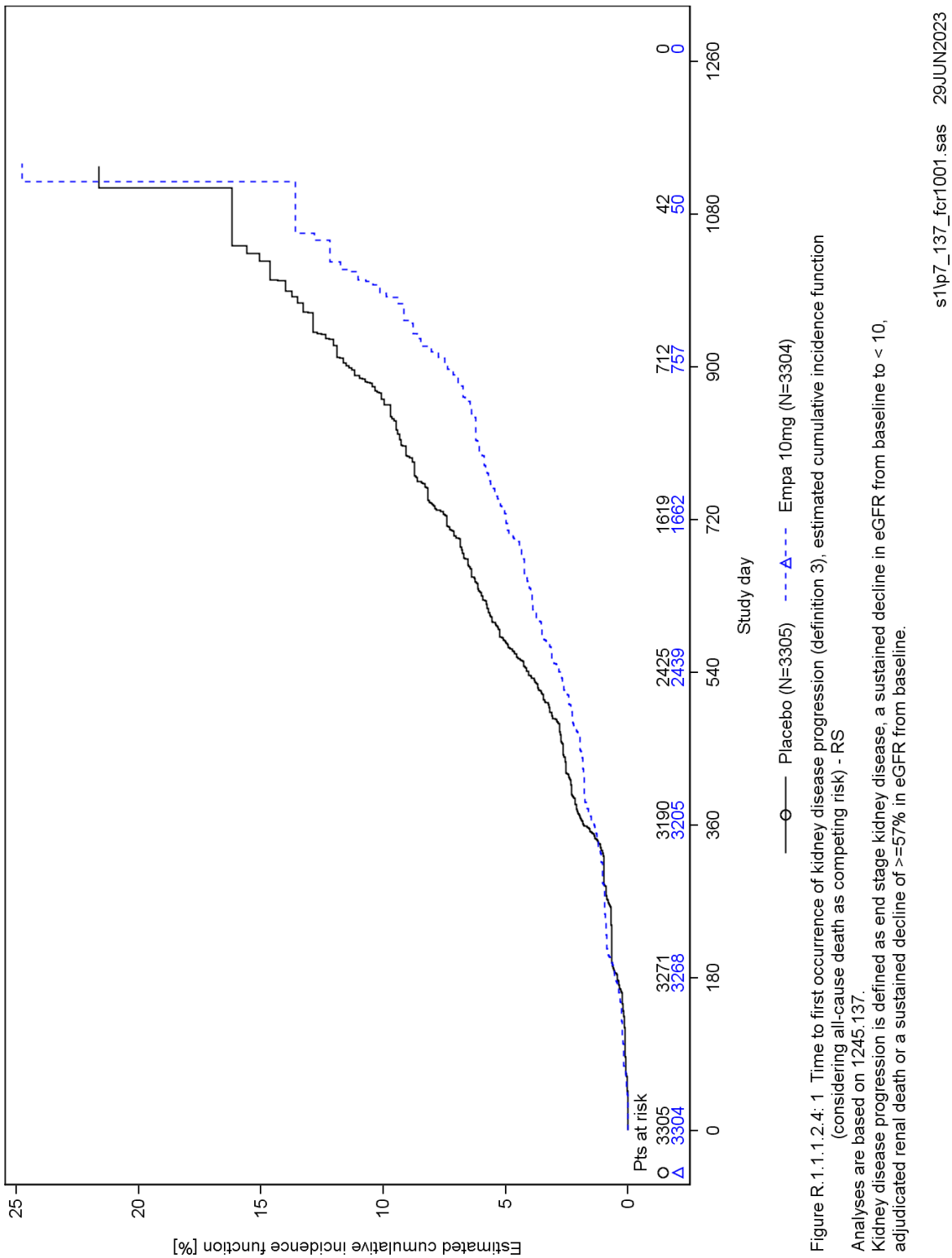


Figure R.1.1.1.2.4: 1 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline to < 10, adjudicated renal death or a sustained decline of >=57% in eGFR from baseline.

R.1.1.1.2.5 Time to first occurrence of sustained decline of >= 40% in eGFR

Table R.1.1.1.2.5: 1 Cox Regression for time to first occurrence of sustained decline of >= 40% in eGFR overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 474 | 14.3 | 7.58 | 3304 | 359 | 10.9 | 5.67 | 0.70 | (0.61,0.81) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.

**Figure R.1.1.1.2.5: 1**

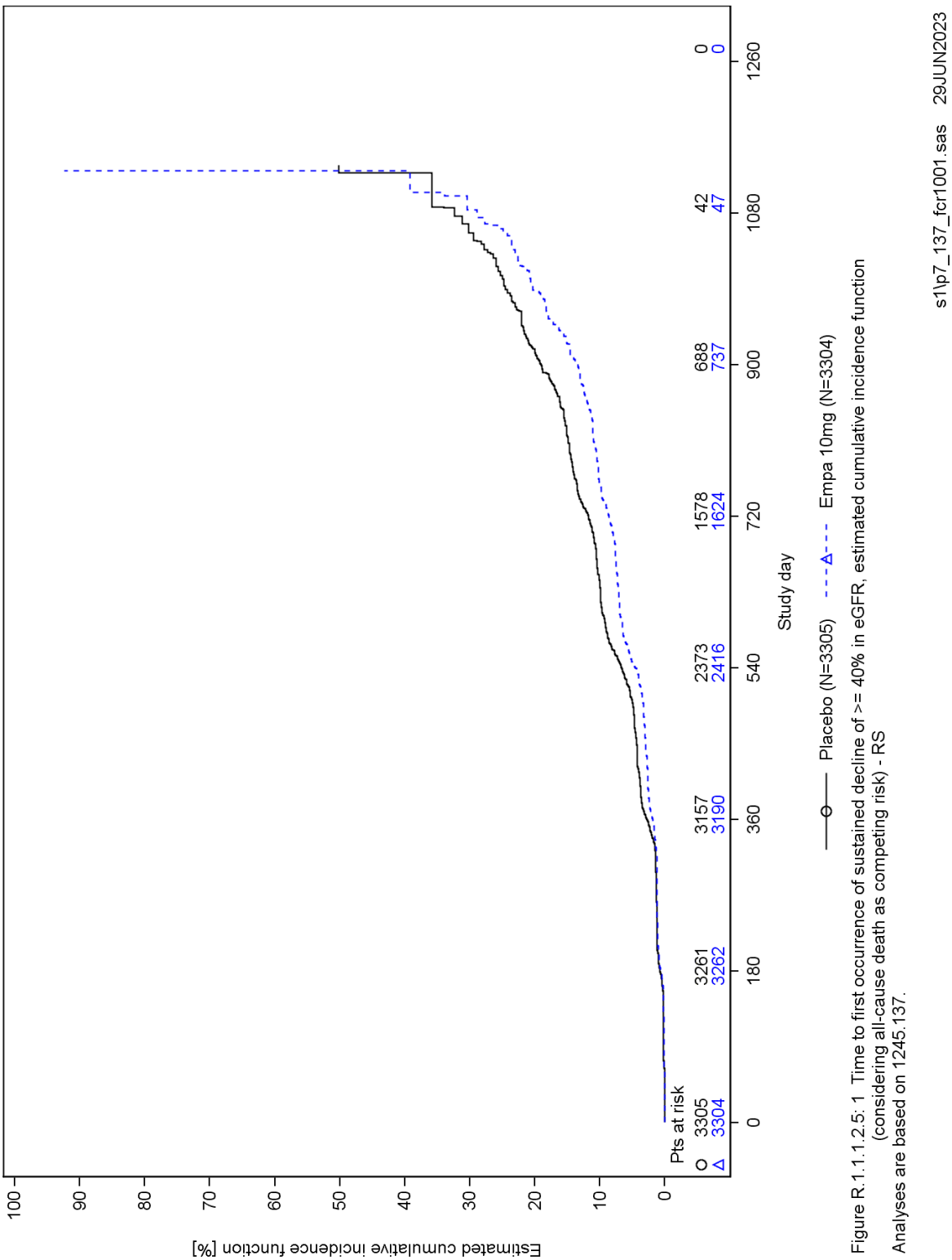


Figure R.1.1.1.2.5: 1 Time to first occurrence of sustained decline of >= 40% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.

R.1.1.1.2.6 Time to first occurrence of sustained decline of >= 50% in eGFR

Table R.1.1.1.2.6: 1 Cox Regression for time to first occurrence of sustained decline of >= 50% in eGFR overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 286 | 8.7 | 4.50 | 3304 | 190 | 5.8 | 2.96 | 0.63 | (0.52,0.75) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.

**Figure R.1.1.1.2.6: 1**

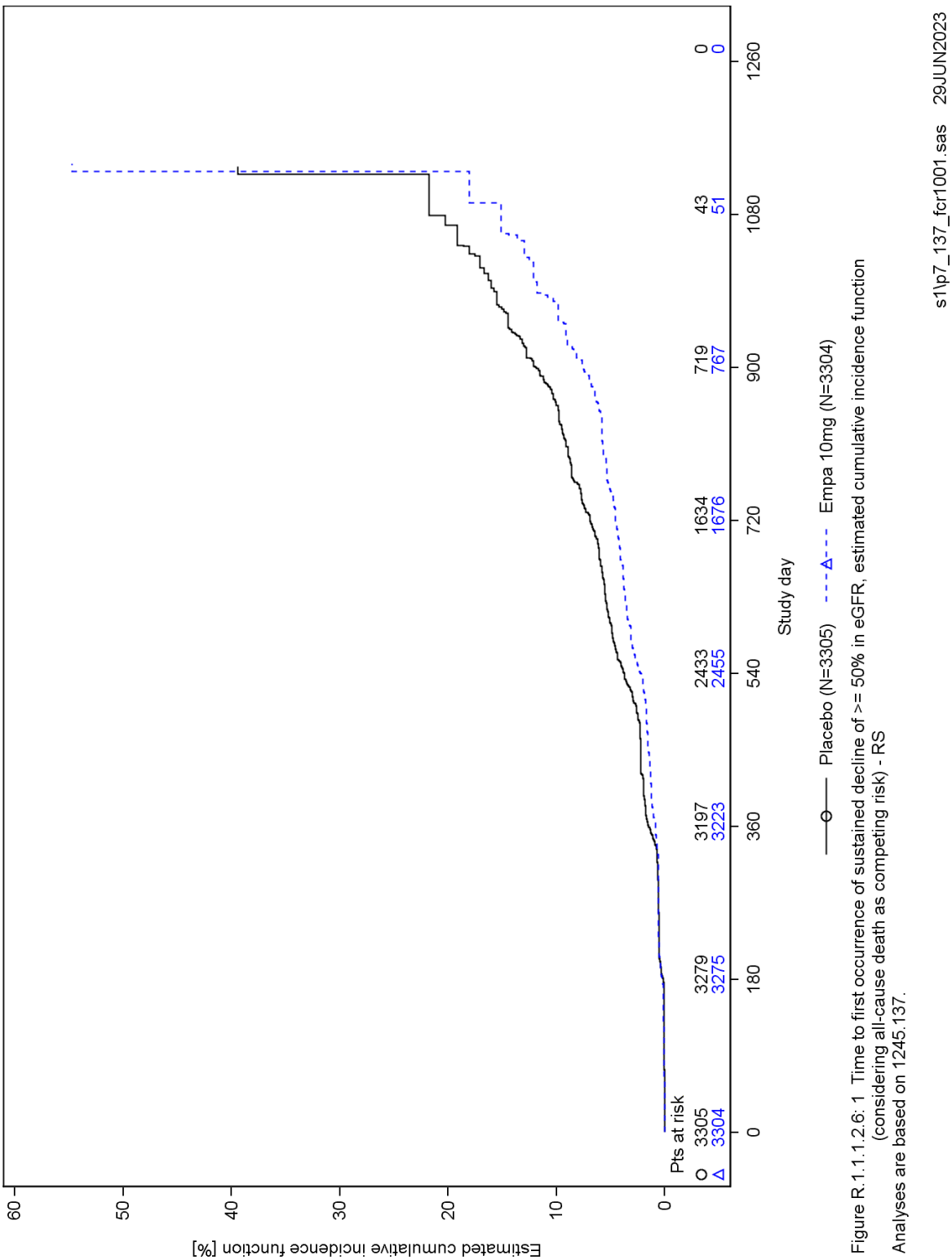


Figure R.1.1.1.2.6: 1 Time to first occurrence of sustained decline of >= 50% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.

R.1.1.1.2.7 Time to first occurrence of sustained decline of >= 57% in eGFR

Table R.1.1.1.2.7: 1 Cox Regression for time to first occurrence of sustained decline of >= 57% in eGFR overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 207 | 6.3 | 3.23 | 3304 | 143 | 4.3 | 2.22 | 0.68 | (0.55,0.85) | 0.0005 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.

**Figure R.1.1.1.2.7: 1**

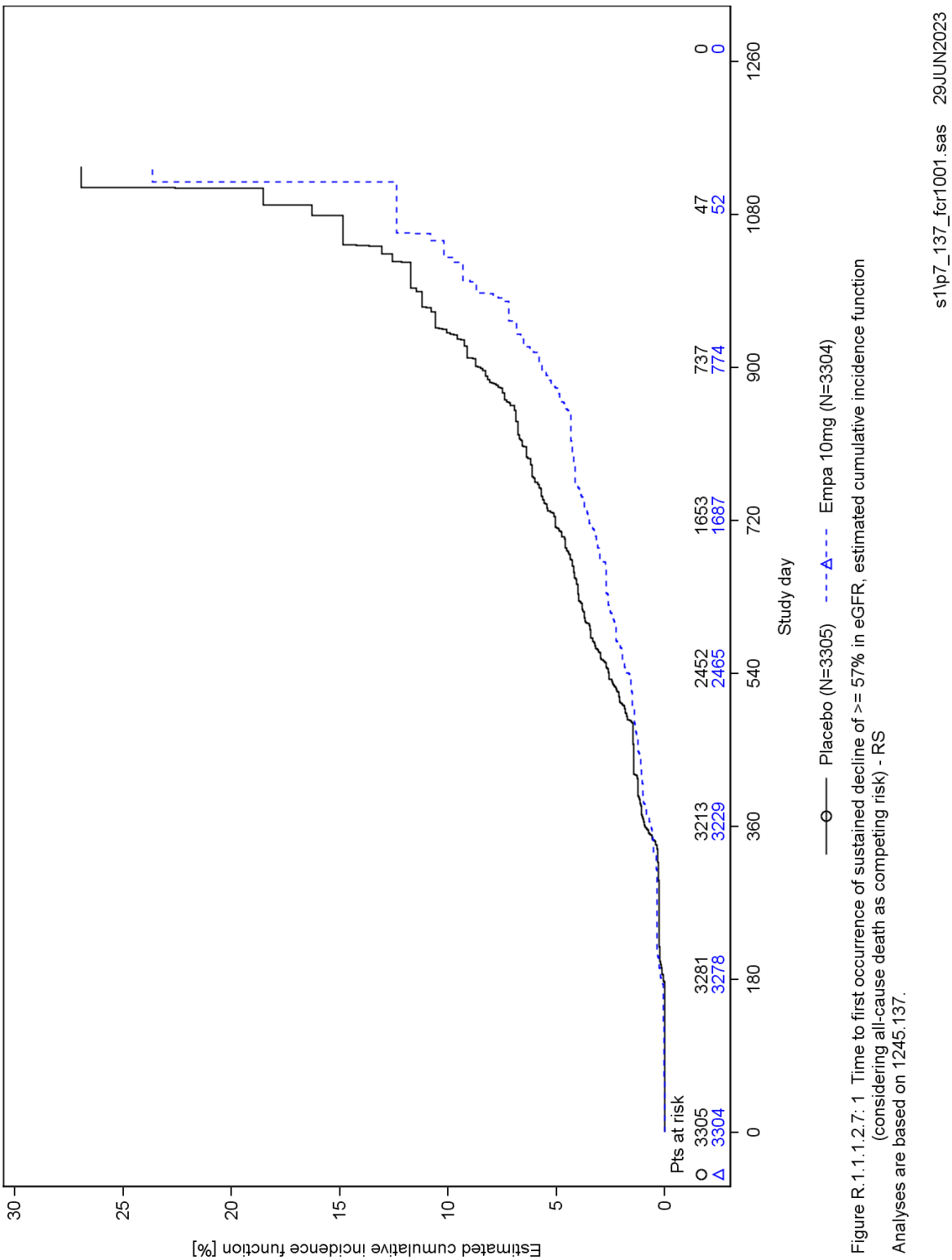


Figure R.1.1.1.2.7: 1 Time to first occurrence of sustained decline of >= 57% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.

**R.1.1.1.2.8**

R.1.1.1.2.8 Time to ESKD

Table R.1.1.1.2.8: 1 Cox Regression for time to ESKD overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 158 | 4.8 | 2.48 | 3304 | 108 | 3.3 | 1.68 | 0.67 | (0.52,0.85) | 0.0012 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.

**Figure R.1.1.1.2.8: 1**

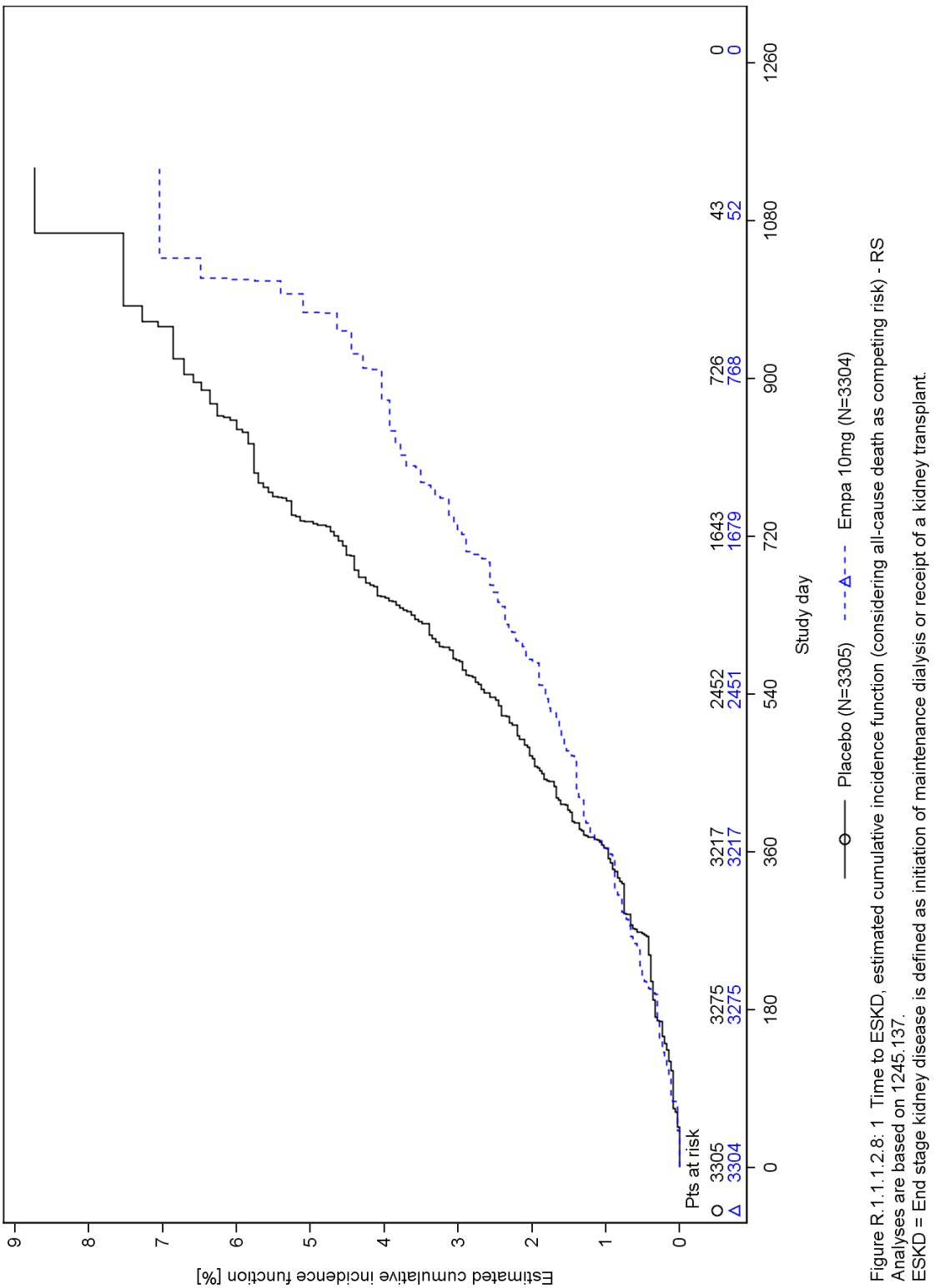


Figure R.1.1.1.2.8: 1 Time to ESKD, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.

R.1.1.1.2.9

R.1.1.1.2.9 Time to first occurrence of ESKD, sustained decline in eGFR to < 10 mL/min/1.73m2 or adjudicated renal death

Table R.1.1.1.2.9: 1 Cox Regression for time to first occurrence of ESKD, sustained decline in eGFR to < 10 mL/min/1.73m2 or adjudicated renal death overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 221 | 6.7 | 3.47 | 3304 | 158 | 4.8 | 2.47 | 0.69 | (0.56,0.85) | 0.0004 | |
| Sex | | | | | | | | | | | | 0.5193 |
| Male | 2210 | 162 | 7.3 | 3.82 | 2207 | 116 | 5.3 | 2.72 | 0.72 | (0.57,0.91) | 0.0068 | |
| Female | 1095 | 59 | 5.4 | 2.79 | 1097 | 42 | 3.8 | 1.97 | 0.62 | (0.41,0.92) | 0.0170 | |
| Age [years] | | | | | | | | | | | | 0.5856 |
| <65 | 1501 | 134 | 8.9 | 4.72 | 1501 | 99 | 6.6 | 3.47 | 0.71 | (0.55,0.93) | 0.0110 | |
| >=65 | 1804 | 87 | 4.8 | 2.47 | 1803 | 59 | 3.3 | 1.66 | 0.63 | (0.46,0.88) | 0.0071 | |
| Region | | | | | | | | | | | | 0.5701 |
| North America | 873 | 57 | 6.5 | 3.55 | 844 | 30 | 3.6 | 1.89 | 0.59 | (0.38,0.92) | 0.0195 | |
| Europe | 1304 | 68 | 5.2 | 2.55 | 1344 | 64 | 4.8 | 2.34 | 0.79 | (0.56,1.11) | 0.1700 | |
| Japan | 308 | 22 | 7.1 | 3.48 | 304 | 10 | 3.3 | 1.61 | 0.48 | (0.23,1.01) | 0.0546 | |
| Other Asia | 820 | 74 | 9.0 | 5.07 | 812 | 54 | 6.7 | 3.69 | 0.72 | (0.51,1.03) | 0.0694 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1646 |
| Diabetic | 1515 | 116 | 7.7 | 3.90 | 1525 | 75 | 4.9 | 2.48 | 0.60 | (0.45,0.80) | 0.0005 | |
| Non-diabetic | 1790 | 105 | 5.9 | 3.10 | 1779 | 83 | 4.7 | 2.46 | 0.80 | (0.60,1.06) | 0.1252 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9951 |
| <30 | 1961 | 134 | 6.8 | 3.63 | 1955 | 101 | 5.2 | 2.71 | 0.68 | (0.53,0.89) | 0.0043 | |
| >=30 | 1337 | 86 | 6.4 | 3.24 | 1340 | 57 | 4.3 | 2.15 | 0.68 | (0.49,0.96) | 0.0267 | |
| Prior CV disease | | | | | | | | | | | | 0.1649 |
| No | 2401 | 157 | 6.5 | 3.40 | 2443 | 127 | 5.2 | 2.69 | 0.75 | (0.59,0.95) | 0.0173 | |
| Yes | 904 | 64 | 7.1 | 3.68 | 861 | 31 | 3.6 | 1.84 | 0.53 | (0.35,0.82) | 0.0039 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5333 |
| <130 | 1208 | 51 | 4.2 | 2.17 | 1190 | 40 | 3.4 | 1.73 | 0.77 | (0.51,1.17) | 0.2281 | |
| >=130 | 2097 | 170 | 8.1 | 4.23 | 2114 | 118 | 5.6 | 2.88 | 0.67 | (0.53,0.84) | 0.0007 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.9: 1 Cox Regression for time to first occurrence of ESKD, sustained decline in eGFR to < 10 mL/min/1.73m2 or adjudicated renal death overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3282 |
| <75 | 1286 | 73 | 5.7 | 2.93 | 1294 | 45 | 3.5 | 1.76 | 0.55 | (0.38,0.79) | 0.0015 | |
| 75 to <85 | 1033 | 71 | 6.9 | 3.53 | 1019 | 51 | 5.0 | 2.57 | 0.77 | (0.54,1.11) | 0.1582 | |
| >=85 | 986 | 77 | 7.8 | 4.15 | 991 | 62 | 6.3 | 3.34 | 0.76 | (0.55,1.07) | 0.1164 | |
| History of heart failure | | | | | | | | | | | | 0.8268 |
| No | 2970 | 205 | 6.9 | 3.59 | 2979 | 146 | 4.9 | 2.53 | 0.69 | (0.55,0.85) | 0.0006 | |
| Yes | 334 | 16 | 4.8 | 2.45 | 324 | 12 | 3.7 | 1.92 | 0.75 | (0.35,1.59) | 0.4507 | |
| History of renal disease | | | | | | | | | | | | 0.8511 |
| Diabetic kidney disease | 1025 | 89 | 8.7 | 4.44 | 1032 | 61 | 5.9 | 3.00 | 0.64 | (0.46,0.88) | 0.0068 | |
| Glomerular disease | 816 | 58 | 7.1 | 3.86 | 853 | 48 | 5.6 | 3.03 | 0.78 | (0.53,1.15) | 0.2060 | |
| Hypertensive/renovascular disease | 739 | 33 | 4.5 | 2.34 | 706 | 25 | 3.5 | 1.79 | 0.73 | (0.43,1.22) | 0.2290 | |
| Other/Unknown | 725 | 41 | 5.7 | 2.84 | 713 | 24 | 3.4 | 1.73 | 0.63 | (0.38,1.05) | 0.0736 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8020 |
| <30 | 1151 | 173 | 15.0 | 8.01 | 1131 | 128 | 11.3 | 5.93 | 0.73 | (0.58,0.91) | 0.0062 | |
| 30 to <45 | 1461 | 41 | 2.8 | 1.42 | 1467 | 25 | 1.7 | 0.87 | 0.60 | (0.37,0.99) | 0.0471 | |
| >=45 | 693 | 7 | 1.0 | 0.53 | 706 | 5 | 0.7 | 0.37 | 0.66 | (0.21,2.09) | 0.4834 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4160 |
| Normal (<30) | 663 | 11 | 1.7 | 0.83 | 665 | 11 | 1.7 | 0.84 | 0.97 | (0.42,2.25) | 0.9515 | |
| Microalbuminuria (30 to <=300) | 937 | 18 | 1.9 | 0.98 | 927 | 16 | 1.7 | 0.88 | 0.95 | (0.49,1.87) | 0.8887 | |
| Macroalbuminuria (>300) | 1705 | 192 | 11.3 | 6.01 | 1712 | 131 | 7.7 | 4.01 | 0.65 | (0.52,0.82) | 0.0002 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3587 |
| Low, moderate or high | 833 | 5 | 0.6 | 0.31 | 839 | 6 | 0.7 | 0.37 | 1.21 | (0.37,3.97) | 0.7525 | |
| Very high | 2472 | 216 | 8.7 | 4.57 | 2465 | 152 | 6.2 | 3.18 | 0.69 | (0.56,0.85) | 0.0004 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.5332 |
| No | 508 | 52 | 10.2 | 5.67 | 473 | 33 | 7.0 | 3.78 | 0.61 | (0.39,0.94) | 0.0255 | |
| Yes | 2797 | 169 | 6.0 | 3.10 | 2831 | 125 | 4.4 | 2.26 | 0.71 | (0.56,0.90) | 0.0039 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.9: 1 Cox Regression for time to first occurrence of ESKD, sustained decline in eGFR to < 10 mL/min/1.73m2 or adjudicated renal death overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.8035 |
| No | 1940 | 125 | 6.4 | 3.38 | 1908 | 86 | 4.5 | 2.35 | 0.67 | (0.51,0.89) | 0.0049 | |
| Yes | 1365 | 96 | 7.0 | 3.61 | 1396 | 72 | 5.2 | 2.63 | 0.71 | (0.52,0.96) | 0.0284 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2898 |
| No | 1852 | 110 | 5.9 | 3.14 | 1942 | 89 | 4.6 | 2.41 | 0.77 | (0.58,1.01) | 0.0631 | |
| Yes | 1453 | 111 | 7.6 | 3.89 | 1362 | 69 | 5.1 | 2.55 | 0.61 | (0.45,0.83) | 0.0016 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.2.9: 1**

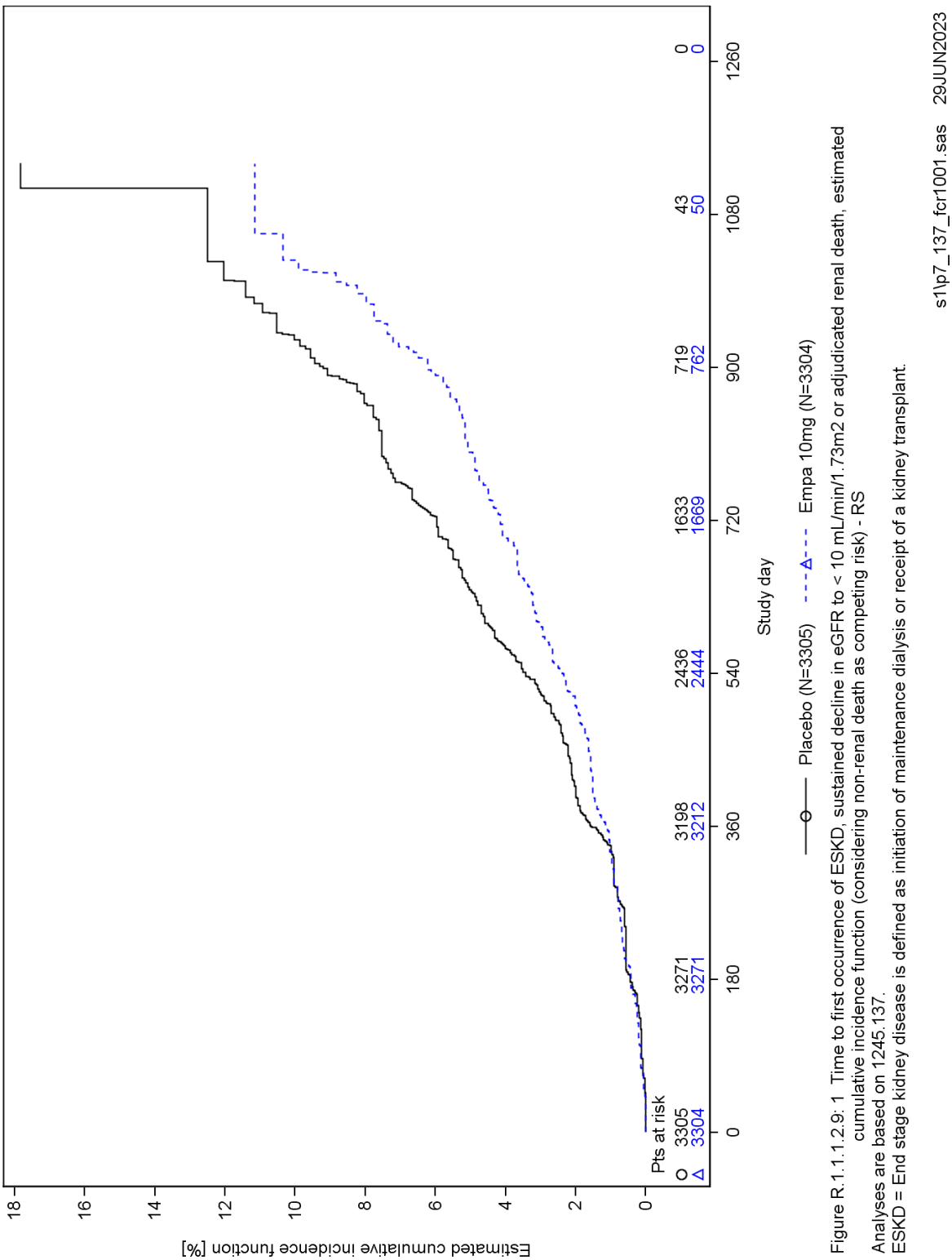


Figure R.1.1.1.2.9: 1 Time to first occurrence of ESKD, sustained decline in eGFR to < 10 mL/min/1.73m2 or adjudicated renal death, estimated cumulative incidence function (considering non-renal death as competing risk) - RS

Analyses are based on 1245.137.

ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.

R.1.1.1.2.10 Time to first occurrence of ESKD or a sustained decline in eGFR to < 10 mL/min/1.73m2

Table R.1.1.1.2.10: 1 Cox Regression for time to first occurrence of ESKD or a sustained decline in eGFR to < 10 mL/min/1.73m2 overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 221 | 6.7 | 3.47 | 3304 | 157 | 4.8 | 2.45 | 0.69 | (0.56,0.84) | 0.0003 | |
| Sex | | | | | | | | | | | | 0.4582 |
| Male | 2210 | 162 | 7.3 | 3.82 | 2207 | 116 | 5.3 | 2.72 | 0.72 | (0.57,0.91) | 0.0068 | |
| Female | 1095 | 59 | 5.4 | 2.79 | 1097 | 41 | 3.7 | 1.92 | 0.60 | (0.40,0.90) | 0.0129 | |
| Age [years] | | | | | | | | | | | | 0.5374 |
| <65 | 1501 | 134 | 8.9 | 4.72 | 1501 | 99 | 6.6 | 3.47 | 0.71 | (0.55,0.93) | 0.0110 | |
| >=65 | 1804 | 87 | 4.8 | 2.47 | 1803 | 58 | 3.2 | 1.64 | 0.62 | (0.45,0.87) | 0.0056 | |
| Region | | | | | | | | | | | | 0.5811 |
| North America | 873 | 57 | 6.5 | 3.55 | 844 | 30 | 3.6 | 1.89 | 0.59 | (0.38,0.92) | 0.0197 | |
| Europe | 1304 | 68 | 5.2 | 2.55 | 1344 | 64 | 4.8 | 2.34 | 0.79 | (0.56,1.11) | 0.1692 | |
| Japan | 308 | 22 | 7.1 | 3.48 | 304 | 10 | 3.3 | 1.61 | 0.48 | (0.23,1.02) | 0.0549 | |
| Other Asia | 820 | 74 | 9.0 | 5.07 | 812 | 53 | 6.5 | 3.62 | 0.71 | (0.50,1.01) | 0.0573 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1460 |
| Diabetic | 1515 | 116 | 7.7 | 3.90 | 1525 | 74 | 4.9 | 2.45 | 0.59 | (0.44,0.79) | 0.0004 | |
| Non-diabetic | 1790 | 105 | 5.9 | 3.10 | 1779 | 83 | 4.7 | 2.46 | 0.80 | (0.60,1.07) | 0.1263 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9710 |
| <30 | 1961 | 134 | 6.8 | 3.63 | 1955 | 100 | 5.1 | 2.68 | 0.68 | (0.52,0.88) | 0.0036 | |
| >=30 | 1337 | 86 | 6.4 | 3.24 | 1340 | 57 | 4.3 | 2.15 | 0.68 | (0.49,0.96) | 0.0267 | |
| Prior CV disease | | | | | | | | | | | | 0.1741 |
| No | 2401 | 157 | 6.5 | 3.40 | 2443 | 126 | 5.2 | 2.67 | 0.75 | (0.59,0.94) | 0.0149 | |
| Yes | 904 | 64 | 7.1 | 3.68 | 861 | 31 | 3.6 | 1.84 | 0.53 | (0.35,0.82) | 0.0039 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5087 |
| <130 | 1208 | 51 | 4.2 | 2.17 | 1190 | 40 | 3.4 | 1.73 | 0.78 | (0.51,1.18) | 0.2301 | |
| >=130 | 2097 | 170 | 8.1 | 4.23 | 2114 | 117 | 5.5 | 2.86 | 0.66 | (0.52,0.84) | 0.0006 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.10: 1 Cox Regression for time to first occurrence of ESKD or a sustained decline in eGFR to < 10 mL/min/1.73m2 overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3477 |
| <75 | 1286 | 73 | 5.7 | 2.93 | 1294 | 45 | 3.5 | 1.76 | 0.55 | (0.38,0.79) | 0.0015 | |
| 75 to <85 | 1033 | 71 | 6.9 | 3.53 | 1019 | 51 | 5.0 | 2.57 | 0.77 | (0.54,1.11) | 0.1594 | |
| >=85 | 986 | 77 | 7.8 | 4.15 | 991 | 61 | 6.2 | 3.28 | 0.75 | (0.54,1.05) | 0.0972 | |
| History of heart failure | | | | | | | | | | | | 0.8165 |
| No | 2970 | 205 | 6.9 | 3.59 | 2979 | 145 | 4.9 | 2.51 | 0.68 | (0.55,0.85) | 0.0005 | |
| Yes | 334 | 16 | 4.8 | 2.45 | 324 | 12 | 3.7 | 1.92 | 0.75 | (0.35,1.58) | 0.4492 | |
| History of renal disease | | | | | | | | | | | | 0.8295 |
| Diabetic kidney disease | 1025 | 89 | 8.7 | 4.44 | 1032 | 60 | 5.8 | 2.95 | 0.63 | (0.45,0.87) | 0.0052 | |
| Glomerular disease | 816 | 58 | 7.1 | 3.86 | 853 | 48 | 5.6 | 3.03 | 0.78 | (0.53,1.15) | 0.2055 | |
| Hypertensive/renovascular disease | 739 | 33 | 4.5 | 2.34 | 706 | 25 | 3.5 | 1.79 | 0.73 | (0.43,1.22) | 0.2301 | |
| Other/Unknown | 725 | 41 | 5.7 | 2.84 | 713 | 24 | 3.4 | 1.73 | 0.63 | (0.38,1.05) | 0.0743 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.7254 |
| <30 | 1151 | 173 | 15.0 | 8.01 | 1131 | 128 | 11.3 | 5.93 | 0.73 | (0.58,0.91) | 0.0063 | |
| 30 to <45 | 1461 | 41 | 2.8 | 1.42 | 1467 | 24 | 1.6 | 0.83 | 0.58 | (0.35,0.96) | 0.0341 | |
| >=45 | 693 | 7 | 1.0 | 0.53 | 706 | 5 | 0.7 | 0.37 | 0.66 | (0.21,2.09) | 0.4831 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4031 |
| Normal (<30) | 663 | 11 | 1.7 | 0.83 | 665 | 11 | 1.7 | 0.84 | 0.97 | (0.42,2.25) | 0.9500 | |
| Microalbuminuria (30 to <=300) | 937 | 18 | 1.9 | 0.98 | 927 | 16 | 1.7 | 0.88 | 0.95 | (0.49,1.87) | 0.8887 | |
| Macroalbuminuria (>300) | 1705 | 192 | 11.3 | 6.01 | 1712 | 130 | 7.6 | 3.98 | 0.65 | (0.52,0.81) | 0.0002 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3528 |
| Low, moderate or high | 833 | 5 | 0.6 | 0.31 | 839 | 6 | 0.7 | 0.37 | 1.21 | (0.37,3.97) | 0.7523 | |
| Very high | 2472 | 216 | 8.7 | 4.57 | 2465 | 151 | 6.1 | 3.16 | 0.68 | (0.56,0.84) | 0.0003 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.4659 |
| No | 508 | 52 | 10.2 | 5.67 | 473 | 32 | 6.8 | 3.66 | 0.59 | (0.38,0.92) | 0.0194 | |
| Yes | 2797 | 169 | 6.0 | 3.10 | 2831 | 125 | 4.4 | 2.26 | 0.71 | (0.56,0.90) | 0.0039 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.10: 1 Cox Regression for time to first occurrence of ESKD or a sustained decline in eGFR to < 10 mL/min/1.73m2 overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.7655 |
| No | 1940 | 125 | 6.4 | 3.38 | 1908 | 85 | 4.5 | 2.32 | 0.67 | (0.50,0.88) | 0.0039 | |
| Yes | 1365 | 96 | 7.0 | 3.61 | 1396 | 72 | 5.2 | 2.63 | 0.71 | (0.52,0.96) | 0.0284 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3154 |
| No | 1852 | 110 | 5.9 | 3.14 | 1942 | 88 | 4.5 | 2.38 | 0.76 | (0.57,1.00) | 0.0539 | |
| Yes | 1453 | 111 | 7.6 | 3.89 | 1362 | 69 | 5.1 | 2.55 | 0.61 | (0.45,0.83) | 0.0016 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.2.10: 1**

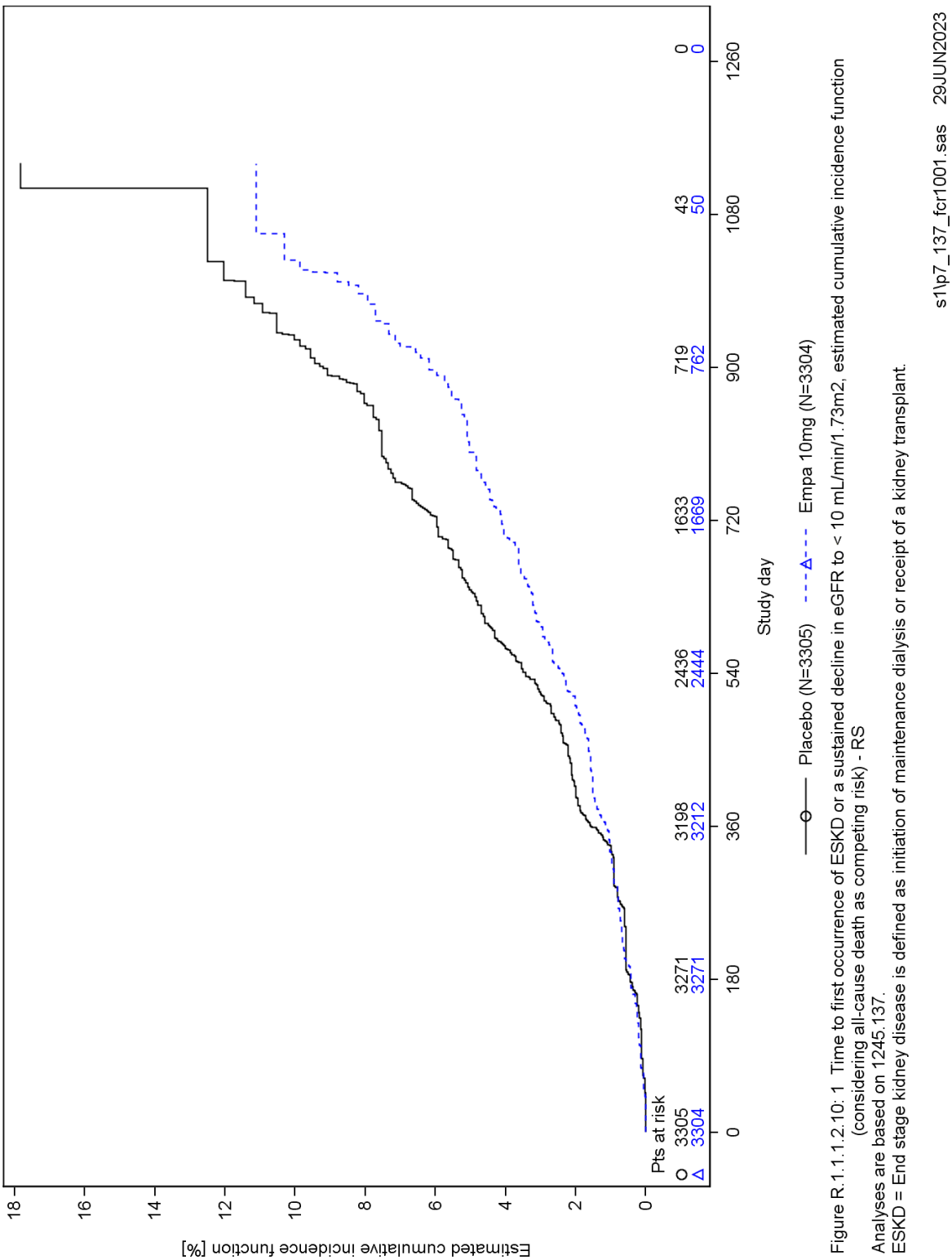


Figure R.1.1.1.2.10: 1 Time to first occurrence of ESKD or a sustained decline in eGFR to < 10 mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.

R.1.1.1.2.11 Time to first occurrence of a sustained decline in eGFR to < 10 mL/min/1.73m2

Table R.1.1.1.2.11: 1 Cox Regression for time to first occurrence of a sustained decline in eGFR to < 10 mL/min/1.73m2 overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 167 | 5.1 | 2.60 | 3304 | 116 | 3.5 | 1.80 | 0.69 | (0.54,0.87) | 0.0021 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.

**Figure R.1.1.1.2.11: 1**

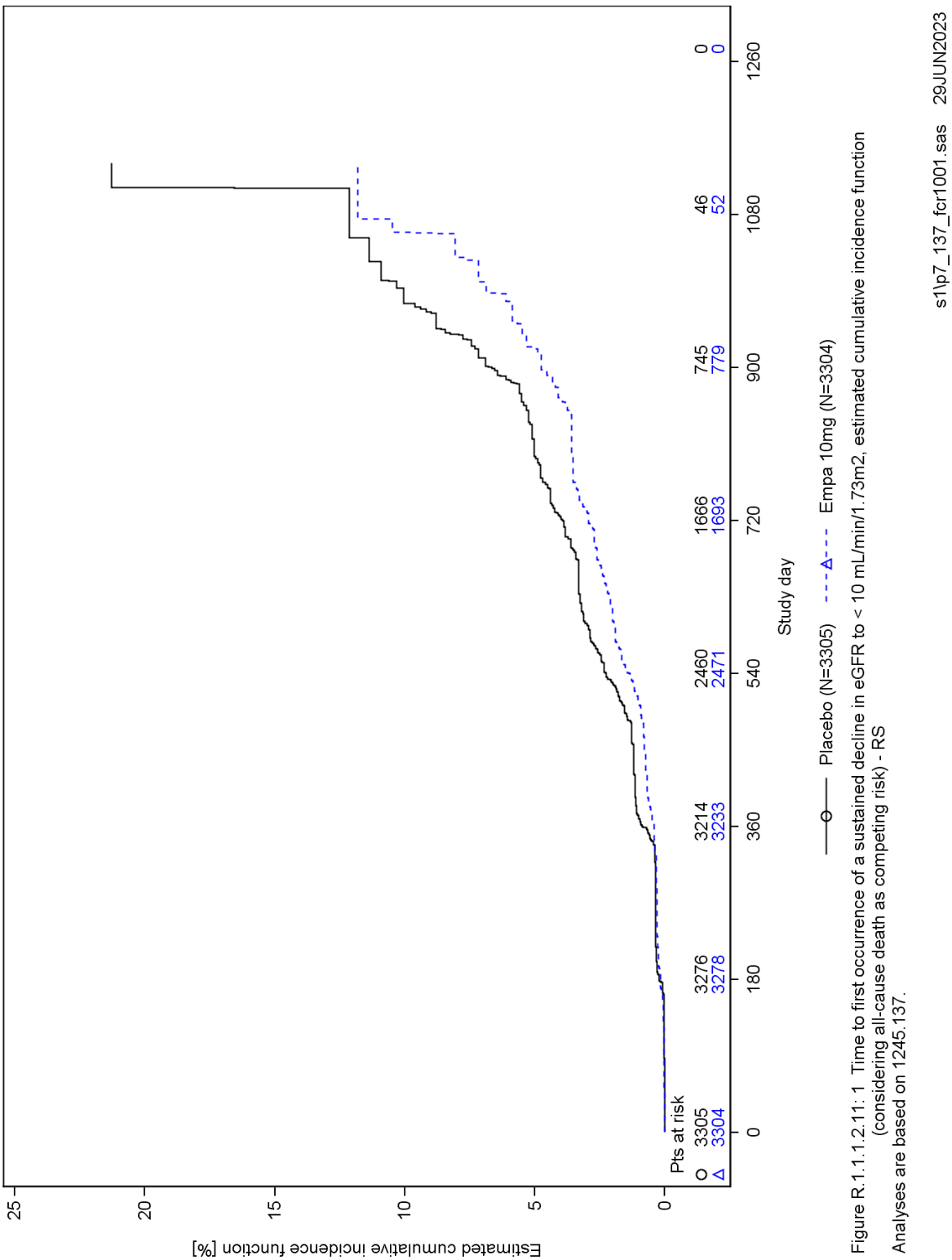


Figure R.1.1.1.2.11: 1 Time to first occurrence of a sustained decline in eGFR to < 10 mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.

R.1.1.1.2.12

R.1.1.1.2.12 Time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2

Table R.1.1.1.2.12: 1 Cox Regression for time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2 overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 387 | 11.7 | 6.21 | 3304 | 308 | 9.3 | 4.89 | 0.73 | (0.63,0.85) | <0.0001 | |
| Sex | | | | | | | | | | | | 0.1581 |
| Male | 2210 | 274 | 12.4 | 6.59 | 2207 | 221 | 10.0 | 5.26 | 0.78 | (0.66,0.94) | 0.0075 | |
| Female | 1095 | 113 | 10.3 | 5.44 | 1097 | 87 | 7.9 | 4.14 | 0.62 | (0.47,0.82) | 0.0008 | |
| Age [years] | | | | | | | | | | | | 0.4745 |
| <65 | 1501 | 210 | 14.0 | 7.56 | 1501 | 170 | 11.3 | 6.07 | 0.76 | (0.62,0.93) | 0.0075 | |
| >=65 | 1804 | 177 | 9.8 | 5.12 | 1803 | 138 | 7.7 | 3.94 | 0.68 | (0.54,0.85) | 0.0007 | |
| Region | | | | | | | | | | | | 0.3050 |
| North America | 873 | 87 | 10.0 | 5.50 | 844 | 62 | 7.3 | 3.94 | 0.76 | (0.55,1.05) | 0.0938 | |
| Europe | 1304 | 133 | 10.2 | 5.08 | 1344 | 125 | 9.3 | 4.66 | 0.80 | (0.63,1.02) | 0.0742 | |
| Japan | 308 | 43 | 14.0 | 6.98 | 304 | 20 | 6.6 | 3.25 | 0.45 | (0.27,0.77) | 0.0037 | |
| Other Asia | 820 | 124 | 15.1 | 8.74 | 812 | 101 | 12.4 | 7.06 | 0.73 | (0.56,0.95) | 0.0208 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.0818 |
| Diabetic | 1515 | 195 | 12.9 | 6.70 | 1525 | 140 | 9.2 | 4.71 | 0.64 | (0.51,0.79) | <0.0001 | |
| Non-diabetic | 1790 | 192 | 10.7 | 5.78 | 1779 | 168 | 9.4 | 5.05 | 0.83 | (0.68,1.02) | 0.0836 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9291 |
| <30 | 1961 | 232 | 11.8 | 6.42 | 1955 | 192 | 9.8 | 5.23 | 0.73 | (0.60,0.88) | 0.0011 | |
| >=30 | 1337 | 153 | 11.4 | 5.87 | 1340 | 116 | 8.7 | 4.44 | 0.74 | (0.58,0.94) | 0.0133 | |
| Prior CV disease | | | | | | | | | | | | 0.3002 |
| No | 2401 | 273 | 11.4 | 6.03 | 2443 | 237 | 9.7 | 5.11 | 0.77 | (0.65,0.92) | 0.0036 | |
| Yes | 904 | 114 | 12.6 | 6.69 | 861 | 71 | 8.2 | 4.28 | 0.64 | (0.48,0.86) | 0.0035 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3716 |
| <130 | 1208 | 95 | 7.9 | 4.09 | 1190 | 78 | 6.6 | 3.43 | 0.82 | (0.61,1.11) | 0.2029 | |
| >=130 | 2097 | 292 | 13.9 | 7.47 | 2114 | 230 | 10.9 | 5.72 | 0.70 | (0.59,0.84) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.12: 1 Cox Regression for time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2 overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4218 |
| <75 | 1286 | 137 | 10.7 | 5.60 | 1294 | 105 | 8.1 | 4.16 | 0.63 | (0.49,0.82) | 0.0005 | |
| 75 to <85 | 1033 | 119 | 11.5 | 6.01 | 1019 | 90 | 8.8 | 4.60 | 0.78 | (0.60,1.03) | 0.0831 | |
| >=85 | 986 | 131 | 13.3 | 7.26 | 991 | 113 | 11.4 | 6.20 | 0.79 | (0.61,1.01) | 0.0612 | |
| History of heart failure | | | | | | | | | | | | 0.8214 |
| No | 2970 | 363 | 12.2 | 6.49 | 2979 | 288 | 9.7 | 5.07 | 0.73 | (0.63,0.85) | <0.0001 | |
| Yes | 334 | 24 | 7.2 | 3.74 | 324 | 20 | 6.2 | 3.23 | 0.78 | (0.43,1.42) | 0.4221 | |
| History of renal disease | | | | | | | | | | | | 0.6781 |
| Diabetic kidney disease | 1025 | 149 | 14.5 | 7.61 | 1032 | 113 | 10.9 | 5.68 | 0.70 | (0.55,0.89) | 0.0041 | |
| Glomerular disease | 816 | 96 | 11.8 | 6.50 | 853 | 86 | 10.1 | 5.51 | 0.84 | (0.63,1.13) | 0.2434 | |
| Hypertensive/renovascular disease | 739 | 65 | 8.8 | 4.69 | 706 | 57 | 8.1 | 4.13 | 0.75 | (0.53,1.08) | 0.1219 | |
| Other/Unknown | 725 | 77 | 10.6 | 5.45 | 713 | 52 | 7.3 | 3.79 | 0.65 | (0.45,0.92) | 0.0153 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.9832 |
| <30 | 1151 | 320 | 27.8 | 15.66 | 1131 | 259 | 22.9 | 12.54 | 0.75 | (0.63,0.88) | 0.0005 | |
| 30 to <45 | 1461 | 57 | 3.9 | 1.98 | 1467 | 41 | 2.8 | 1.43 | 0.72 | (0.48,1.07) | 0.1054 | |
| >=45 | 693 | 10 | 1.4 | 0.76 | 706 | 8 | 1.1 | 0.59 | 0.75 | (0.30,1.91) | 0.5483 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.3378 |
| Normal (<30) | 663 | 24 | 3.6 | 1.82 | 665 | 19 | 2.9 | 1.45 | 0.76 | (0.41,1.38) | 0.3633 | |
| Microalbuminuria (30 to <=300) | 937 | 35 | 3.7 | 1.91 | 927 | 34 | 3.7 | 1.88 | 1.04 | (0.65,1.67) | 0.8694 | |
| Macroalbuminuria (>300) | 1705 | 328 | 19.2 | 10.64 | 1712 | 255 | 14.9 | 8.02 | 0.71 | (0.61,0.84) | <0.0001 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.8403 |
| Low, moderate or high | 833 | 7 | 0.8 | 0.43 | 839 | 6 | 0.7 | 0.37 | 0.86 | (0.29,2.57) | 0.7934 | |
| Very high | 2472 | 380 | 15.4 | 8.27 | 2465 | 302 | 12.3 | 6.46 | 0.77 | (0.66,0.90) | 0.0008 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.5429 |
| No | 508 | 82 | 16.1 | 9.18 | 473 | 60 | 12.7 | 7.05 | 0.67 | (0.48,0.93) | 0.0168 | |
| Yes | 2797 | 305 | 10.9 | 5.71 | 2831 | 248 | 8.8 | 4.55 | 0.75 | (0.63,0.88) | 0.0007 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.2.12: 1 Cox Regression for time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2 overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6935 |
| No | 1940 | 218 | 11.2 | 6.01 | 1908 | 165 | 8.6 | 4.57 | 0.71 | (0.58,0.87) | 0.0010 | |
| Yes | 1365 | 169 | 12.4 | 6.48 | 1396 | 143 | 10.2 | 5.32 | 0.76 | (0.60,0.95) | 0.0144 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9874 |
| No | 1852 | 212 | 11.4 | 6.18 | 1942 | 174 | 9.0 | 4.78 | 0.73 | (0.60,0.90) | 0.0025 | |
| Yes | 1453 | 175 | 12.0 | 6.25 | 1362 | 134 | 9.8 | 5.03 | 0.73 | (0.58,0.92) | 0.0067 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.2.12: 1**

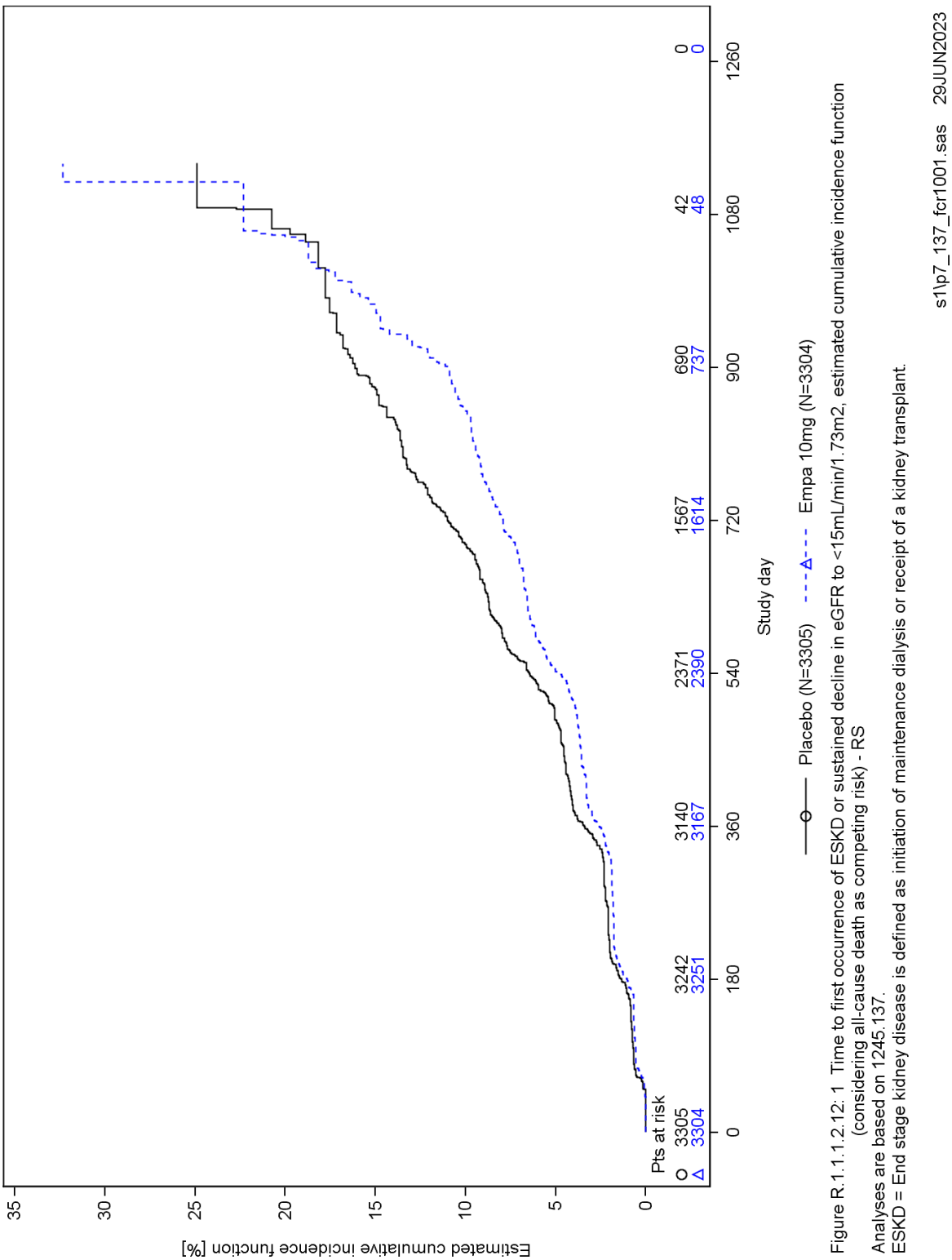


Figure R.1.1.1.2.12: 1 Time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.137.
ESKD = End stage kidney disease is defined as initiation of maintenance dialysis or receipt of a kidney transplant.

R.1.1.1.2.13 Time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2

Table R.1.1.1.2.13: 1 Cox Regression for time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2 overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 360 | 10.9 | 5.76 | 3304 | 290 | 8.8 | 4.58 | 0.73 | (0.62,0.85) | <0.0001 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.

**Figure R.1.1.1.2.13: 1**

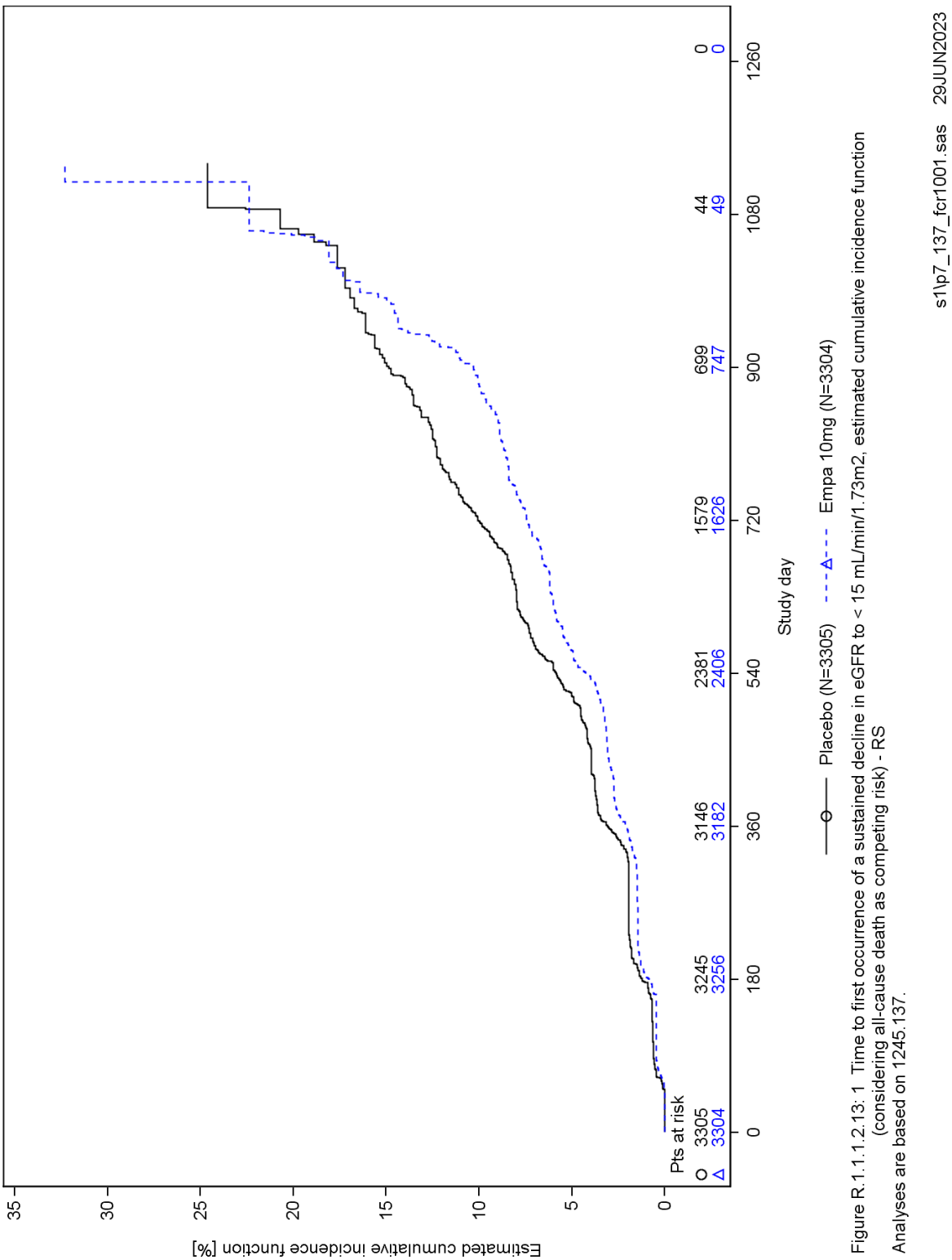


Figure R.1.1.1.2.13: 1 Time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.

**R.1.1.1.2.14**

R.1.1.1.2.14 Time to first occurrence of adjudicated acute kidney injury

Table R.1.1.1.2.14: 1 Cox Regression for time to first occurrence of adjudicated acute kidney injury overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 135 | 4.1 | 2.11 | 3304 | 107 | 3.2 | 1.67 | 0.78 | (0.60,1.00) | 0.0545 | |
| Sex | | | | | | | | | | | | 0.1636 |
| Male | 2210 | 100 | 4.5 | 2.35 | 2207 | 71 | 3.2 | 1.66 | 0.69 | (0.51,0.94) | 0.0183 | |
| Female | 1095 | 35 | 3.2 | 1.65 | 1097 | 36 | 3.3 | 1.70 | 1.03 | (0.65,1.64) | 0.9012 | |
| Age [years] | | | | | | | | | | | | 0.8782 |
| <65 | 1501 | 47 | 3.1 | 1.64 | 1501 | 38 | 2.5 | 1.32 | 0.80 | (0.52,1.23) | 0.3151 | |
| >=65 | 1804 | 88 | 4.9 | 2.50 | 1803 | 69 | 3.8 | 1.96 | 0.77 | (0.56,1.06) | 0.1048 | |
| Region | | | | | | | | | | | | 0.7962 |
| North America | 873 | 45 | 5.2 | 2.81 | 844 | 37 | 4.4 | 2.35 | 0.84 | (0.54,1.30) | 0.4360 | |
| Europe | 1304 | 58 | 4.4 | 2.18 | 1344 | 48 | 3.6 | 1.76 | 0.79 | (0.54,1.16) | 0.2228 | |
| Japan | 308 | 4 | 1.3 | 0.62 | 304 | 1 | 0.3 | 0.16 | 0.28 | (0.03,2.48) | 0.2512 | |
| Other Asia | 820 | 28 | 3.4 | 1.89 | 812 | 21 | 2.6 | 1.43 | 0.73 | (0.42,1.29) | 0.2809 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2286 |
| Diabetic | 1515 | 81 | 5.3 | 2.72 | 1525 | 73 | 4.8 | 2.43 | 0.88 | (0.64,1.20) | 0.4126 | |
| Non-diabetic | 1790 | 54 | 3.0 | 1.59 | 1779 | 34 | 1.9 | 1.00 | 0.63 | (0.41,0.97) | 0.0356 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1273 |
| <30 | 1961 | 65 | 3.3 | 1.75 | 1955 | 41 | 2.1 | 1.09 | 0.62 | (0.42,0.92) | 0.0169 | |
| >=30 | 1337 | 70 | 5.2 | 2.64 | 1340 | 66 | 4.9 | 2.51 | 0.93 | (0.66,1.30) | 0.6628 | |
| Prior CV disease | | | | | | | | | | | | 0.6003 |
| No | 2401 | 76 | 3.2 | 1.63 | 2443 | 59 | 2.4 | 1.24 | 0.74 | (0.53,1.04) | 0.0878 | |
| Yes | 904 | 59 | 6.5 | 3.40 | 861 | 48 | 5.6 | 2.90 | 0.85 | (0.58,1.25) | 0.4118 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0824 |
| <130 | 1208 | 37 | 3.1 | 1.58 | 1190 | 38 | 3.2 | 1.66 | 1.09 | (0.69,1.71) | 0.7153 | |
| >=130 | 2097 | 98 | 4.7 | 2.42 | 2114 | 69 | 3.3 | 1.68 | 0.67 | (0.49,0.91) | 0.0107 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Acute kidney injury is defined based on adjudication results.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1.

Table R.1.1.1.2.14: 1 Cox Regression for time to first occurrence of adjudicated acute kidney injury overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5650 |
| <75 | 1286 | 61 | 4.7 | 2.44 | 1294 | 55 | 4.3 | 2.17 | 0.87 | (0.61,1.26) | 0.4719 | |
| 75 to <85 | 1033 | 44 | 4.3 | 2.18 | 1019 | 27 | 2.6 | 1.36 | 0.63 | (0.39,1.02) | 0.0593 | |
| >=85 | 986 | 30 | 3.0 | 1.60 | 991 | 25 | 2.5 | 1.33 | 0.80 | (0.47,1.35) | 0.3998 | |
| History of heart failure | | | | | | | | | | | | 0.0335 |
| No | 2970 | 113 | 3.8 | 1.97 | 2979 | 78 | 2.6 | 1.35 | 0.68 | (0.51,0.90) | 0.0082 | |
| Yes | 334 | 22 | 6.6 | 3.39 | 324 | 29 | 9.0 | 4.77 | 1.34 | (0.77,2.33) | 0.3070 | |
| History of renal disease | | | | | | | | | | | | 0.2789 |
| Diabetic kidney disease | 1025 | 61 | 6.0 | 3.03 | 1032 | 49 | 4.7 | 2.42 | 0.77 | (0.53,1.12) | 0.1761 | |
| Glomerular disease | 816 | 20 | 2.5 | 1.31 | 853 | 12 | 1.4 | 0.75 | 0.57 | (0.28,1.17) | 0.1250 | |
| Hypertensive/renovascular disease | 739 | 28 | 3.8 | 2.00 | 706 | 17 | 2.4 | 1.22 | 0.60 | (0.33,1.10) | 0.0983 | |
| Other/Unknown | 725 | 26 | 3.6 | 1.80 | 713 | 29 | 4.1 | 2.11 | 1.19 | (0.70,2.01) | 0.5293 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2179 |
| <30 | 1151 | 63 | 5.5 | 2.84 | 1131 | 60 | 5.3 | 2.75 | 0.96 | (0.67,1.36) | 0.8055 | |
| 30 to <45 | 1461 | 57 | 3.9 | 2.00 | 1467 | 40 | 2.7 | 1.40 | 0.69 | (0.46,1.03) | 0.0688 | |
| >=45 | 693 | 15 | 2.2 | 1.15 | 706 | 7 | 1.0 | 0.52 | 0.45 | (0.18,1.11) | 0.0843 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.3962 |
| Normal (<30) | 663 | 17 | 2.6 | 1.29 | 665 | 17 | 2.6 | 1.30 | 1.02 | (0.52,2.00) | 0.9472 | |
| Microalbuminuria (30 to <=300) | 937 | 41 | 4.4 | 2.26 | 927 | 37 | 4.0 | 2.06 | 0.90 | (0.58,1.40) | 0.6360 | |
| Macroalbuminuria (>300) | 1705 | 77 | 4.5 | 2.37 | 1712 | 53 | 3.1 | 1.61 | 0.66 | (0.47,0.94) | 0.0210 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4785 |
| Low, moderate or high | 833 | 17 | 2.0 | 1.04 | 839 | 10 | 1.2 | 0.62 | 0.60 | (0.27,1.30) | 0.1957 | |
| Very high | 2472 | 118 | 4.8 | 2.48 | 2465 | 97 | 3.9 | 2.03 | 0.80 | (0.62,1.05) | 0.1136 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.4187 |
| No | 508 | 27 | 5.3 | 2.89 | 473 | 16 | 3.4 | 1.83 | 0.62 | (0.33,1.15) | 0.1295 | |
| Yes | 2797 | 108 | 3.9 | 1.98 | 2831 | 91 | 3.2 | 1.65 | 0.82 | (0.62,1.08) | 0.1629 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Acute kidney injury is defined based on adjudication results.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1.

Table R.1.1.1.2.14: 1 Cox Regression for time to first occurrence of adjudicated acute kidney injury overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5355 |
| No | 1940 | 59 | 3.0 | 1.58 | 1908 | 41 | 2.1 | 1.11 | 0.70 | (0.47,1.05) | 0.0852 | |
| Yes | 1365 | 76 | 5.6 | 2.87 | 1396 | 66 | 4.7 | 2.43 | 0.83 | (0.60,1.15) | 0.2686 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.4250 |
| No | 1852 | 47 | 2.5 | 1.33 | 1942 | 45 | 2.3 | 1.22 | 0.90 | (0.60,1.35) | 0.6086 | |
| Yes | 1453 | 88 | 6.1 | 3.08 | 1362 | 62 | 4.6 | 2.30 | 0.73 | (0.52,1.01) | 0.0541 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Acute kidney injury is defined based on adjudication results.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1.

**Figure R.1.1.1.2.14: 1**

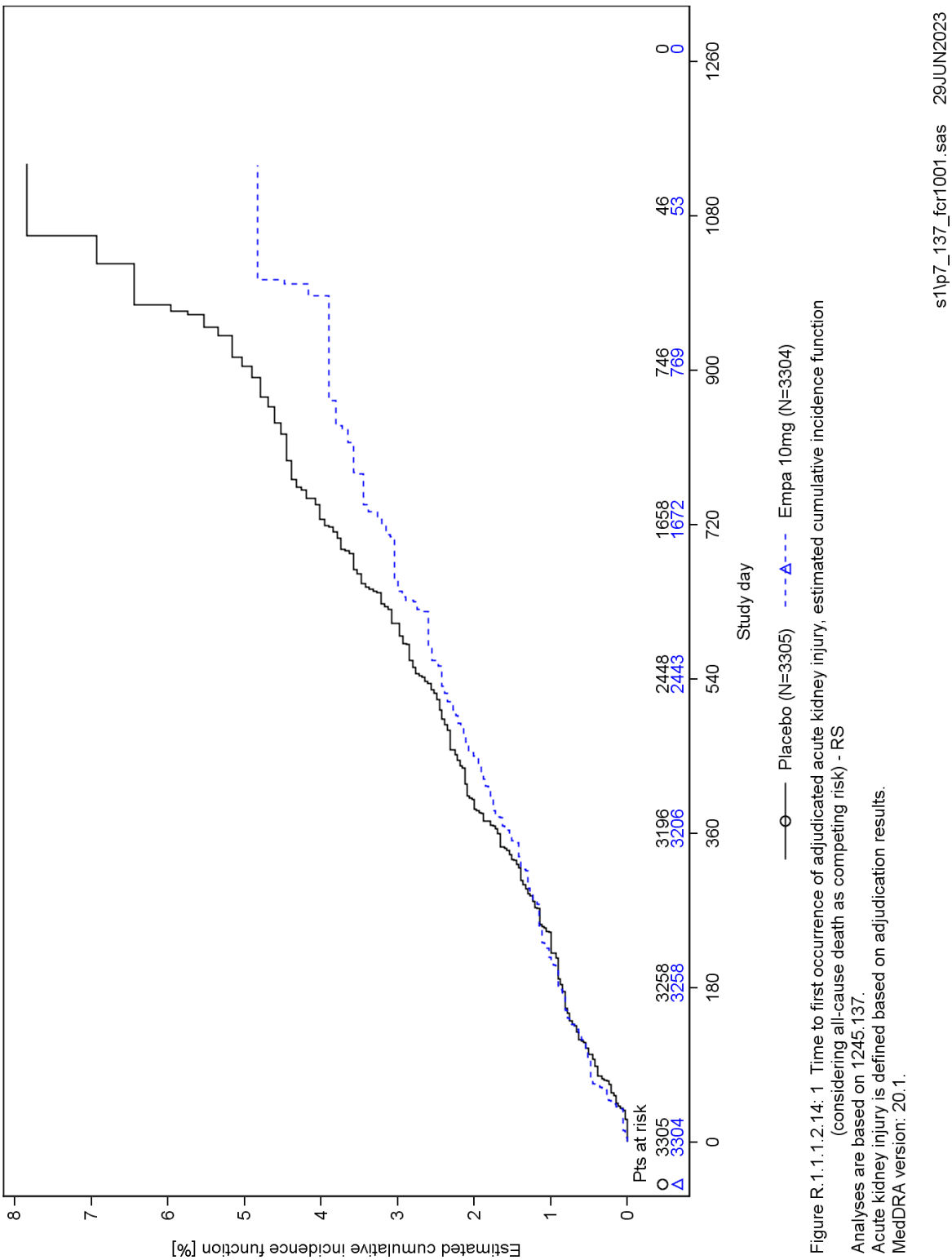


Figure R.1.1.1.2.14: 1 Time to first occurrence of adjudicated acute kidney injury, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.137.
Acute kidney injury is defined based on adjudication results.
MedDRA version: 20.1.

**Figure R.1.1.1.2.14: 2**

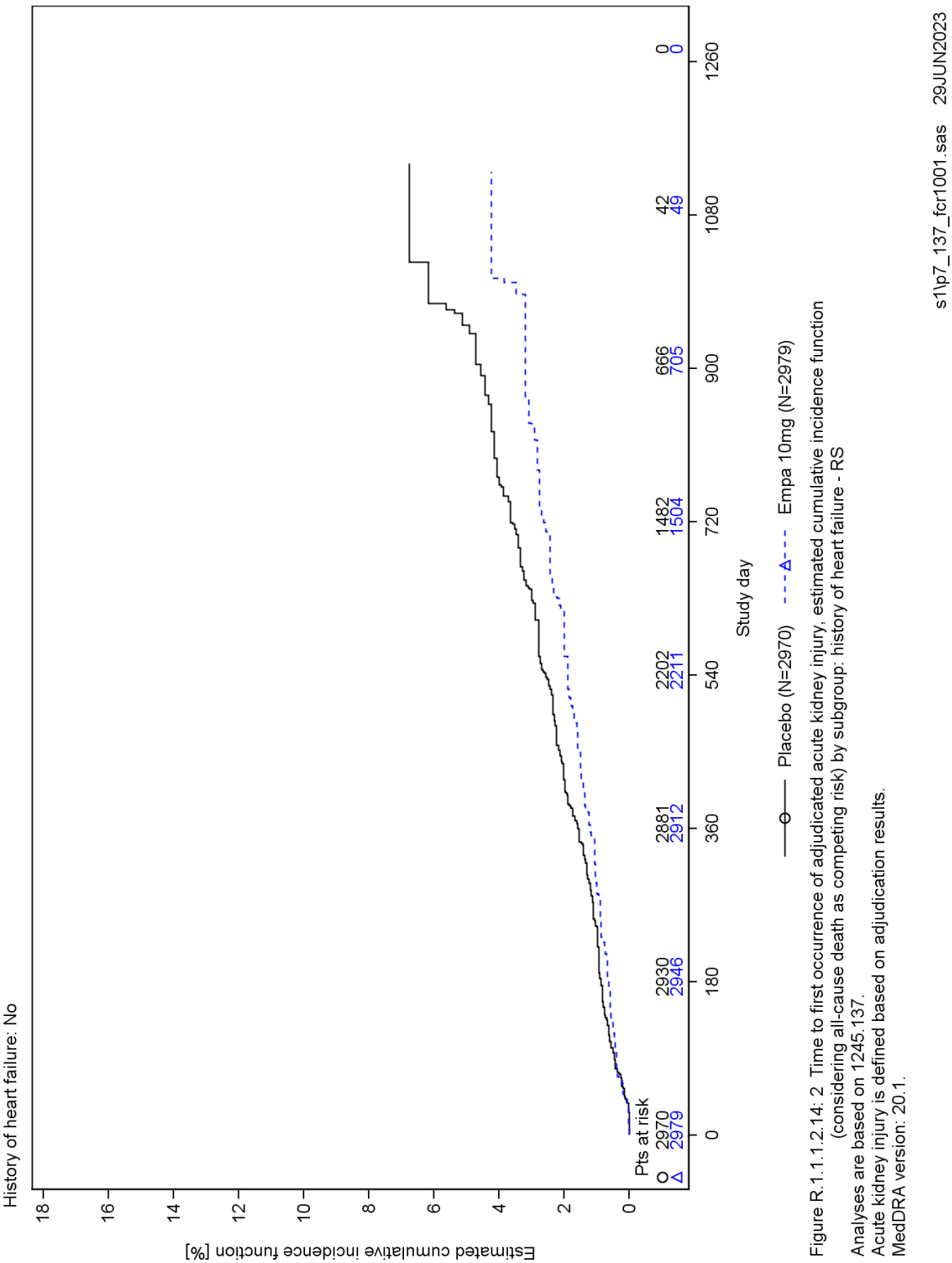


Figure R.1.1.1.2.14: 2 Time to first occurrence of adjudicated acute kidney injury, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: history of heart failure - RS

Analyses are based on 1245.137.
Acute kidney injury is defined based on adjudication results.
MedDRA version: 20.1.

**Figure R.1.1.1.2.14: 2**

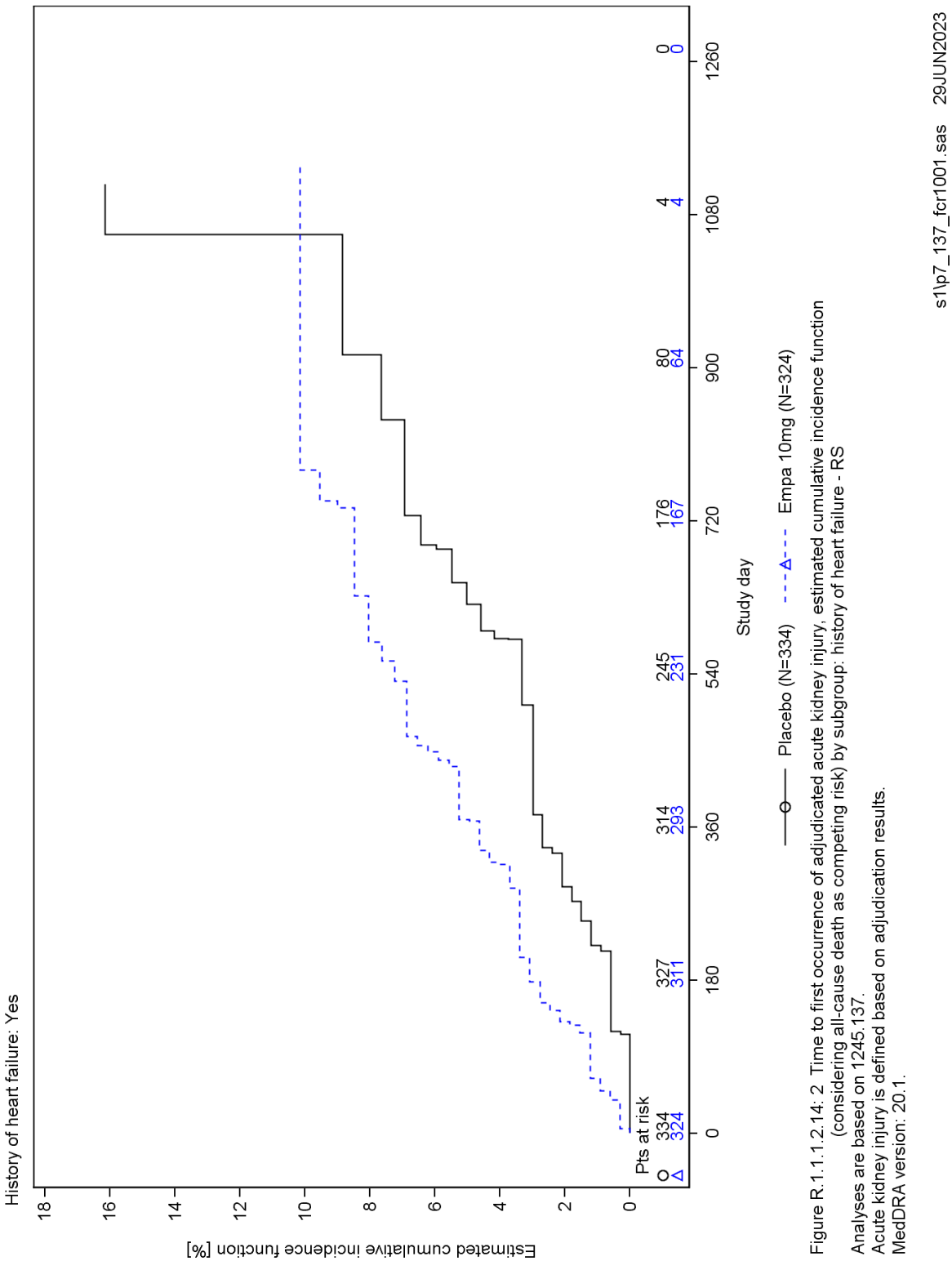


Figure R.1.1.1.2.14: 2 Time to first occurrence of adjudicated acute kidney injury, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: history of heart failure - RS

Analyses are based on 1245.137.
Acute kidney injury is defined based on adjudication results.
MedDRA version: 20.1.

**R.1.1.1.2.15**

R.1.1.1.2.15 Time to initiation of maintainance dialysis

Table R.1.1.1.2.15: 1 Cox Regression for time to initiation of maintenance dialysis overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 152 | 4.6 | 2.38 | 3304 | 103 | 3.1 | 1.60 | 0.66 | (0.51,0.84) | 0.0010 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.

**Figure R.1.1.1.2.15: 1**

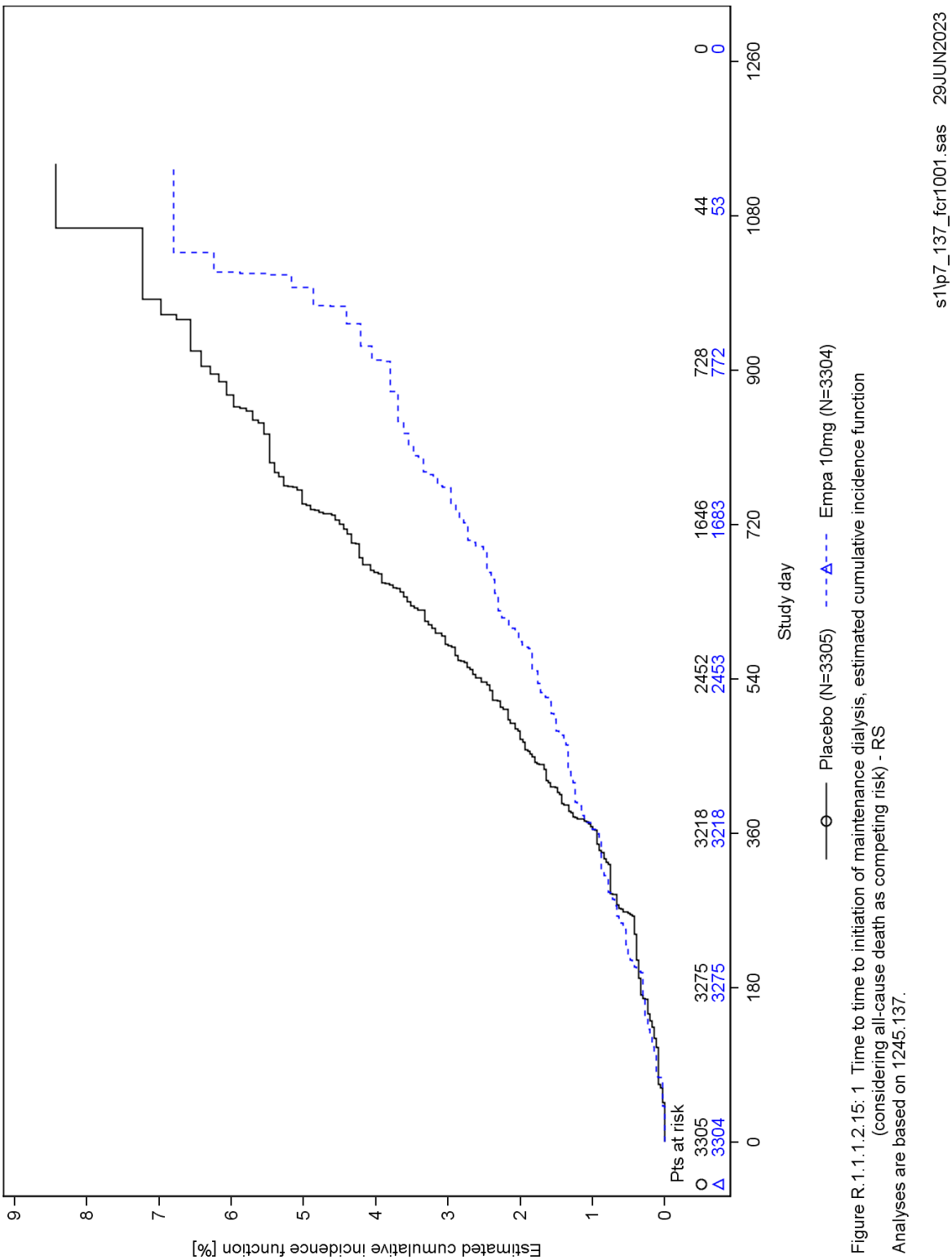


Figure R.1.1.1.2.15: 1 Time to time to initiation of maintenance dialysis, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.

**R.1.1.1.2.16**

R.1.1.1.2.16 Time to receipt of kidney transplant

Table R.1.1.1.2.16: 1 Cox Regression for time to receipt of kidney transplant overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 9 | 0.3 | 0.14 | 3304 | 10 | 0.3 | 0.15 | 1.08 | (0.43,2.73) | 0.8731 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.

**Figure R.1.1.1.2.16: 1**

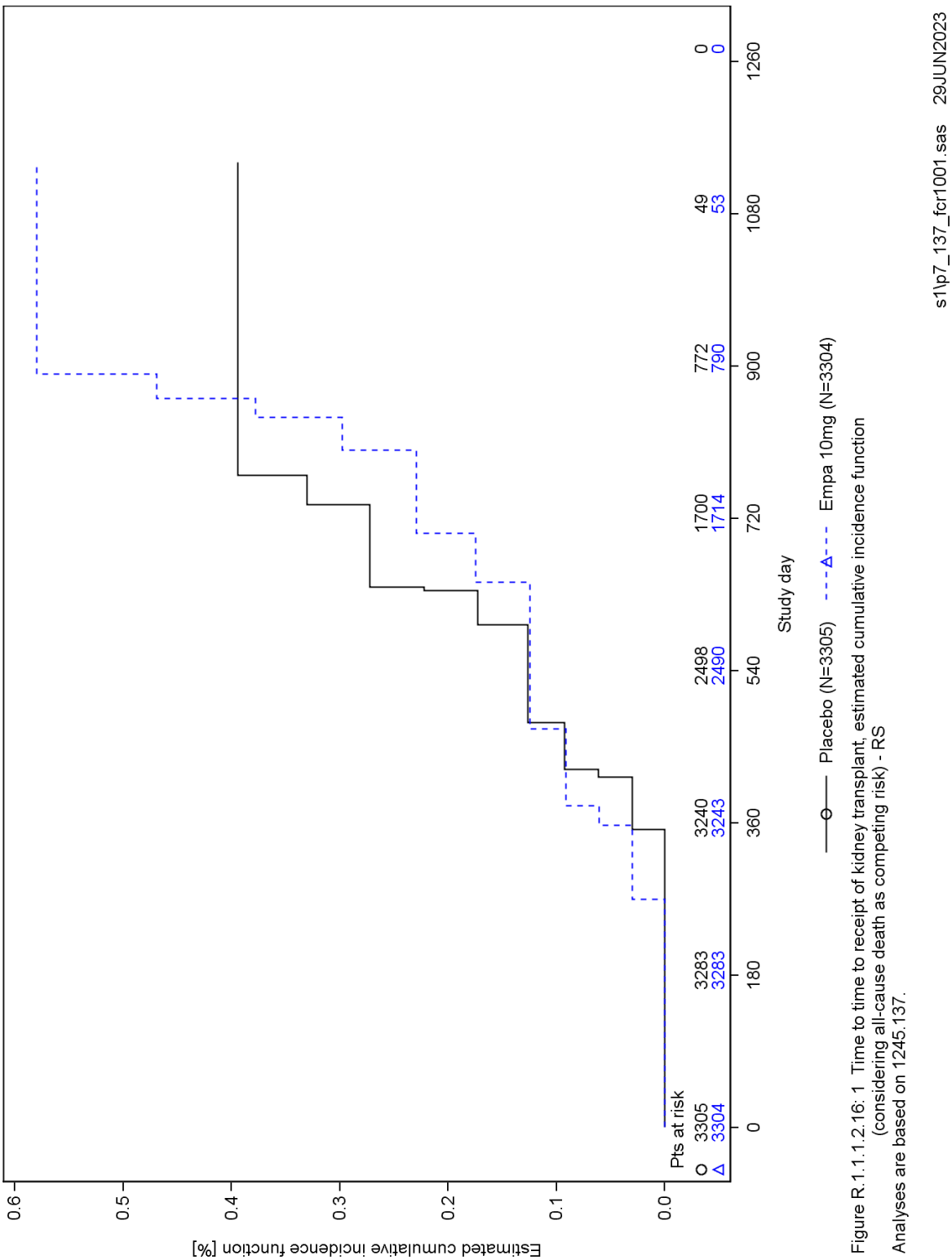


Figure R.1.1.1.2.16: 1 Time to time to receipt of kidney transplant, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.

**R.1.1.1.3**

R.1.1.1.3.1 Time to first occurrence of an adjudicated major cardiovascular event

Table R.1.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 213 | 6.4 | 3.36 | 3304 | 200 | 6.1 | 3.15 | 0.93 | (0.76,1.12) | 0.4349 | |
| Sex | | | | | | | | | | | | 0.9848 |
| Male | 2210 | 162 | 7.3 | 3.83 | 2207 | 151 | 6.8 | 3.56 | 0.93 | (0.74,1.16) | 0.4923 | |
| Female | 1095 | 51 | 4.7 | 2.41 | 1097 | 49 | 4.5 | 2.31 | 0.93 | (0.63,1.38) | 0.7140 | |
| Age [years] | | | | | | | | | | | | 0.6758 |
| <65 | 1501 | 51 | 3.4 | 1.77 | 1501 | 53 | 3.5 | 1.84 | 1.00 | (0.68,1.47) | 0.9974 | |
| >=65 | 1804 | 162 | 9.0 | 4.68 | 1803 | 147 | 8.2 | 4.23 | 0.91 | (0.73,1.14) | 0.4081 | |
| Region | | | | | | | | | | | | 0.4820 |
| North America | 873 | 61 | 7.0 | 3.80 | 844 | 53 | 6.3 | 3.35 | 0.88 | (0.61,1.27) | 0.4941 | |
| Europe | 1304 | 105 | 8.1 | 3.99 | 1344 | 93 | 6.9 | 3.44 | 0.84 | (0.63,1.11) | 0.2158 | |
| Japan | 308 | 15 | 4.9 | 2.37 | 304 | 13 | 4.3 | 2.11 | 1.00 | (0.47,2.10) | 0.9943 | |
| Other Asia | 820 | 32 | 3.9 | 2.17 | 812 | 41 | 5.0 | 2.82 | 1.28 | (0.80,2.03) | 0.2989 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2417 |
| Diabetic | 1515 | 156 | 10.3 | 5.32 | 1525 | 138 | 9.0 | 4.65 | 0.86 | (0.68,1.08) | 0.1934 | |
| Non-diabetic | 1790 | 57 | 3.2 | 1.67 | 1779 | 62 | 3.5 | 1.83 | 1.11 | (0.77,1.59) | 0.5754 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0986 |
| <30 | 1961 | 92 | 4.7 | 2.49 | 1955 | 100 | 5.1 | 2.69 | 1.10 | (0.83,1.46) | 0.5026 | |
| >=30 | 1337 | 120 | 9.0 | 4.56 | 1340 | 99 | 7.4 | 3.78 | 0.79 | (0.61,1.04) | 0.0893 | |
| Prior CV disease | | | | | | | | | | | | 0.3940 |
| No | 2401 | 89 | 3.7 | 1.91 | 2443 | 96 | 3.9 | 2.03 | 1.04 | (0.78,1.39) | 0.7931 | |
| Yes | 904 | 124 | 13.7 | 7.35 | 861 | 104 | 12.1 | 6.38 | 0.88 | (0.68,1.14) | 0.3265 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7385 |
| <130 | 1208 | 72 | 6.0 | 3.11 | 1190 | 62 | 5.2 | 2.71 | 0.88 | (0.63,1.24) | 0.4752 | |
| >=130 | 2097 | 141 | 6.7 | 3.50 | 2114 | 138 | 6.5 | 3.40 | 0.95 | (0.75,1.20) | 0.6561 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3425 |
| <75 | 1286 | 113 | 8.8 | 4.60 | 1294 | 110 | 8.5 | 4.38 | 0.93 | (0.72,1.22) | 0.6149 | |
| 75 to <85 | 1033 | 52 | 5.0 | 2.57 | 1019 | 54 | 5.3 | 2.74 | 1.10 | (0.75,1.60) | 0.6407 | |
| >=85 | 986 | 48 | 4.9 | 2.57 | 991 | 36 | 3.6 | 1.92 | 0.71 | (0.46,1.10) | 0.1259 | |
| History of heart failure | | | | | | | | | | | | 0.9446 |
| No | 2970 | 160 | 5.4 | 2.80 | 2979 | 151 | 5.1 | 2.63 | 0.93 | (0.75,1.17) | 0.5394 | |
| Yes | 334 | 53 | 15.9 | 8.44 | 324 | 49 | 15.1 | 8.12 | 0.92 | (0.62,1.35) | 0.6665 | |
| History of renal disease | | | | | | | | | | | | 0.7261 |
| Diabetic kidney disease | 1025 | 106 | 10.3 | 5.34 | 1032 | 93 | 9.0 | 4.63 | 0.85 | (0.64,1.12) | 0.2422 | |
| Glomerular disease | 816 | 15 | 1.8 | 0.98 | 853 | 17 | 2.0 | 1.06 | 1.10 | (0.55,2.20) | 0.7970 | |
| Hypertensive/renovascular disease | 739 | 46 | 6.2 | 3.30 | 706 | 50 | 7.1 | 3.65 | 1.10 | (0.73,1.64) | 0.6571 | |
| Other/Unknown | 725 | 46 | 6.3 | 3.21 | 713 | 40 | 5.6 | 2.91 | 0.90 | (0.59,1.37) | 0.6156 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6372 |
| <30 | 1151 | 92 | 8.0 | 4.18 | 1131 | 90 | 8.0 | 4.15 | 0.98 | (0.73,1.31) | 0.9020 | |
| 30 to <45 | 1461 | 98 | 6.7 | 3.45 | 1467 | 84 | 5.7 | 2.96 | 0.84 | (0.63,1.13) | 0.2510 | |
| >=45 | 693 | 23 | 3.3 | 1.77 | 706 | 26 | 3.7 | 1.93 | 1.10 | (0.63,1.92) | 0.7471 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.5900 |
| Normal (<30) | 663 | 35 | 5.3 | 2.68 | 665 | 39 | 5.9 | 3.01 | 1.14 | (0.72,1.80) | 0.5724 | |
| Microalbuminuria (30 to <=300) | 937 | 70 | 7.5 | 3.89 | 927 | 64 | 6.9 | 3.59 | 0.90 | (0.64,1.27) | 0.5599 | |
| Macroalbuminuria (>300) | 1705 | 108 | 6.3 | 3.34 | 1712 | 97 | 5.7 | 2.96 | 0.86 | (0.66,1.14) | 0.2993 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4220 |
| Low, moderate or high | 833 | 33 | 4.0 | 2.05 | 839 | 36 | 4.3 | 2.24 | 1.11 | (0.69,1.77) | 0.6762 | |
| Very high | 2472 | 180 | 7.3 | 3.80 | 2465 | 164 | 6.7 | 3.46 | 0.89 | (0.72,1.11) | 0.3021 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.6066 |
| No | 508 | 41 | 8.1 | 4.43 | 473 | 32 | 6.8 | 3.68 | 0.83 | (0.52,1.32) | 0.4338 | |
| Yes | 2797 | 172 | 6.1 | 3.18 | 2831 | 168 | 5.9 | 3.06 | 0.95 | (0.77,1.18) | 0.6389 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.2328 |
| No | 1940 | 80 | 4.1 | 2.15 | 1908 | 81 | 4.2 | 2.22 | 1.06 | (0.78,1.45) | 0.7047 | |
| Yes | 1365 | 133 | 9.7 | 5.08 | 1396 | 119 | 8.5 | 4.40 | 0.83 | (0.65,1.07) | 0.1507 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.0832 |
| No | 1852 | 64 | 3.5 | 1.82 | 1942 | 79 | 4.1 | 2.15 | 1.19 | (0.85,1.65) | 0.3118 | |
| Yes | 1453 | 149 | 10.3 | 5.27 | 1362 | 121 | 8.9 | 4.53 | 0.83 | (0.65,1.05) | 0.1197 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.3.1: 1**

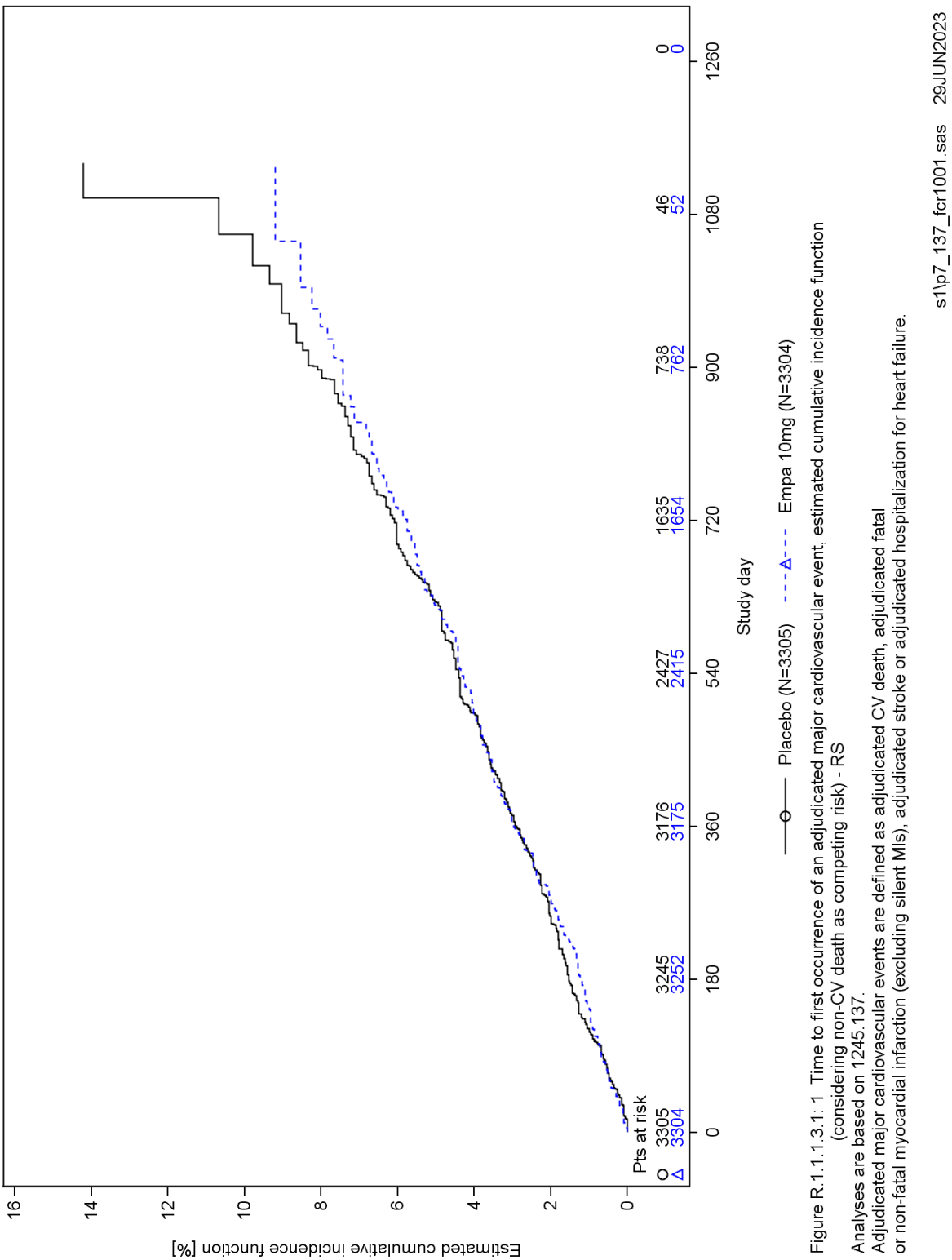


Figure R.1.1.1.3.1: 1 Time to first occurrence of an adjudicated major cardiovascular event, estimated cumulative incidence function (considering non-CV death as competing risk) - RS

Analyses are based on 1245.137.
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.

R.1.1.1.3.2 Time to first occurrence of an adjudicated myocardial infarction

Table R.1.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 44 | 1.3 | 0.68 | 3304 | 49 | 1.5 | 0.76 | 1.10 | (0.73, 1.66) | 0.6348 | |
| Sex | | | | | | | | | | | | 0.6070 |
| Male | 2210 | 36 | 1.6 | 0.84 | 2207 | 38 | 1.7 | 0.88 | 1.05 | (0.66, 1.65) | 0.8483 | |
| Female | 1095 | 8 | 0.7 | 0.37 | 1097 | 11 | 1.0 | 0.51 | 1.37 | (0.55, 3.40) | 0.5019 | |
| Age [years] | | | | | | | | | | | | 0.5173 |
| <65 | 1501 | 13 | 0.9 | 0.45 | 1501 | 18 | 1.2 | 0.62 | 1.35 | (0.66, 2.75) | 0.4114 | |
| >=65 | 1804 | 31 | 1.7 | 0.88 | 1803 | 31 | 1.7 | 0.87 | 1.01 | (0.61, 1.66) | 0.9637 | |
| Region | | | | | | | | | | | | 0.2495 |
| North America | 873 | 17 | 1.9 | 1.04 | 844 | 12 | 1.4 | 0.75 | 0.72 | (0.35, 1.52) | 0.3940 | |
| Europe | 1304 | 18 | 1.4 | 0.67 | 1344 | 19 | 1.4 | 0.69 | 0.99 | (0.52, 1.89) | 0.9778 | |
| Japan | 308 | 3 | 1.0 | 0.47 | 304 | 3 | 1.0 | 0.48 | 1.17 | (0.24, 5.82) | 0.8454 | |
| Other Asia | 820 | 6 | 0.7 | 0.40 | 812 | 15 | 1.8 | 1.02 | 2.47 | (0.96, 6.36) | 0.0616 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1792 |
| Diabetic | 1515 | 33 | 2.2 | 1.10 | 1525 | 31 | 2.0 | 1.02 | 0.91 | (0.56, 1.49) | 0.7155 | |
| Non-diabetic | 1790 | 11 | 0.6 | 0.32 | 1779 | 18 | 1.0 | 0.53 | 1.69 | (0.80, 3.58) | 0.1714 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.8244 |
| <30 | 1961 | 23 | 1.2 | 0.61 | 1955 | 24 | 1.2 | 0.64 | 1.05 | (0.59, 1.87) | 0.8573 | |
| >=30 | 1337 | 21 | 1.6 | 0.78 | 1340 | 25 | 1.9 | 0.94 | 1.16 | (0.65, 2.07) | 0.6251 | |
| Prior CV disease | | | | | | | | | | | | 0.9822 |
| No | 2401 | 23 | 1.0 | 0.49 | 2443 | 27 | 1.1 | 0.57 | 1.13 | (0.65, 1.97) | 0.6716 | |
| Yes | 904 | 21 | 2.3 | 1.20 | 861 | 22 | 2.6 | 1.31 | 1.12 | (0.61, 2.03) | 0.7160 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1082 |
| <130 | 1208 | 17 | 1.4 | 0.72 | 1190 | 11 | 0.9 | 0.48 | 0.66 | (0.31, 1.40) | 0.2784 | |
| >=130 | 2097 | 27 | 1.3 | 0.66 | 2114 | 38 | 1.8 | 0.92 | 1.38 | (0.84, 2.26) | 0.2003 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Includes fatal and non-fatal MIs. Silent MIs are excluded.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2556 |
| <75 | 1286 | 27 | 2.1 | 1.08 | 1294 | 24 | 1.9 | 0.94 | 0.85 | (0.49, 1.47) | 0.5491 | |
| 75 to <85 | 1033 | 8 | 0.8 | 0.39 | 1019 | 15 | 1.5 | 0.75 | 2.00 | (0.85, 4.73) | 0.1141 | |
| >=85 | 986 | 9 | 0.9 | 0.48 | 991 | 10 | 1.0 | 0.53 | 1.08 | (0.44, 2.66) | 0.8693 | |
| History of heart failure | | | | | | | | | | | | 0.9961 |
| No | 2970 | 37 | 1.2 | 0.64 | 2979 | 41 | 1.4 | 0.70 | 1.10 | (0.71, 1.72) | 0.6638 | |
| Yes | 334 | 7 | 2.1 | 1.06 | 324 | 8 | 2.5 | 1.28 | 1.11 | (0.40, 3.06) | 0.8447 | |
| History of renal disease | | | | | | | | | | | | 0.0445 |
| Diabetic kidney disease | 1025 | 25 | 2.4 | 1.23 | 1032 | 18 | 1.7 | 0.88 | 0.69 | (0.38, 1.27) | 0.2341 | |
| Glomerular disease | 816 | 2 | 0.2 | 0.13 | 853 | 10 | 1.2 | 0.62 | 4.68 | (1.02,21.40) | 0.0464 | |
| Hypertensive/renovascular disease | 739 | 8 | 1.1 | 0.57 | 706 | 15 | 2.1 | 1.08 | 1.96 | (0.83, 4.62) | 0.1258 | |
| Other/Unknown | 725 | 9 | 1.2 | 0.62 | 713 | 6 | 0.8 | 0.43 | 0.71 | (0.25, 2.01) | 0.5234 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.0723 |
| <30 | 1151 | 28 | 2.4 | 1.25 | 1131 | 19 | 1.7 | 0.86 | 0.69 | (0.38, 1.24) | 0.2116 | |
| 30 to <45 | 1461 | 12 | 0.8 | 0.41 | 1467 | 21 | 1.4 | 0.73 | 1.72 | (0.84, 3.49) | 0.1354 | |
| >=45 | 693 | 4 | 0.6 | 0.30 | 706 | 9 | 1.3 | 0.67 | 2.17 | (0.67, 7.06) | 0.1972 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.5464 |
| Normal (<30) | 663 | 2 | 0.3 | 0.15 | 665 | 5 | 0.8 | 0.38 | 2.55 | (0.50,13.17) | 0.2626 | |
| Microalbuminuria (30 to <=300) | 937 | 17 | 1.8 | 0.93 | 927 | 16 | 1.7 | 0.88 | 0.94 | (0.48, 1.87) | 0.8648 | |
| Macroalbuminuria (>300) | 1705 | 25 | 1.5 | 0.76 | 1712 | 28 | 1.6 | 0.84 | 1.09 | (0.64, 1.88) | 0.7425 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.1496 |
| Low, moderate or high | 833 | 1 | 0.1 | 0.06 | 839 | 5 | 0.6 | 0.31 | 5.06 | (0.59,43.34) | 0.1387 | |
| Very high | 2472 | 43 | 1.7 | 0.89 | 2465 | 44 | 1.8 | 0.91 | 1.01 | (0.67, 1.54) | 0.9497 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.1151 |
| No | 508 | 13 | 2.6 | 1.38 | 473 | 7 | 1.5 | 0.79 | 0.58 | (0.23, 1.45) | 0.2432 | |
| Yes | 2797 | 31 | 1.1 | 0.56 | 2831 | 42 | 1.5 | 0.76 | 1.32 | (0.83, 2.11) | 0.2361 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Includes fatal and non-fatal MIs. Silent MIs are excluded.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3157 |
| No | 1940 | 18 | 0.9 | 0.48 | 1908 | 24 | 1.3 | 0.65 | 1.39 | (0.75, 2.56) | 0.2954 | |
| Yes | 1365 | 26 | 1.9 | 0.97 | 1396 | 25 | 1.8 | 0.91 | 0.91 | (0.52, 1.58) | 0.7358 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2996 |
| No | 1852 | 17 | 0.9 | 0.48 | 1942 | 25 | 1.3 | 0.67 | 1.41 | (0.76, 2.62) | 0.2728 | |
| Yes | 1453 | 27 | 1.9 | 0.93 | 1362 | 24 | 1.8 | 0.88 | 0.91 | (0.53, 1.58) | 0.7414 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
Includes fatal and non-fatal MIs. Silent MIs are excluded.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.3.2: 1**

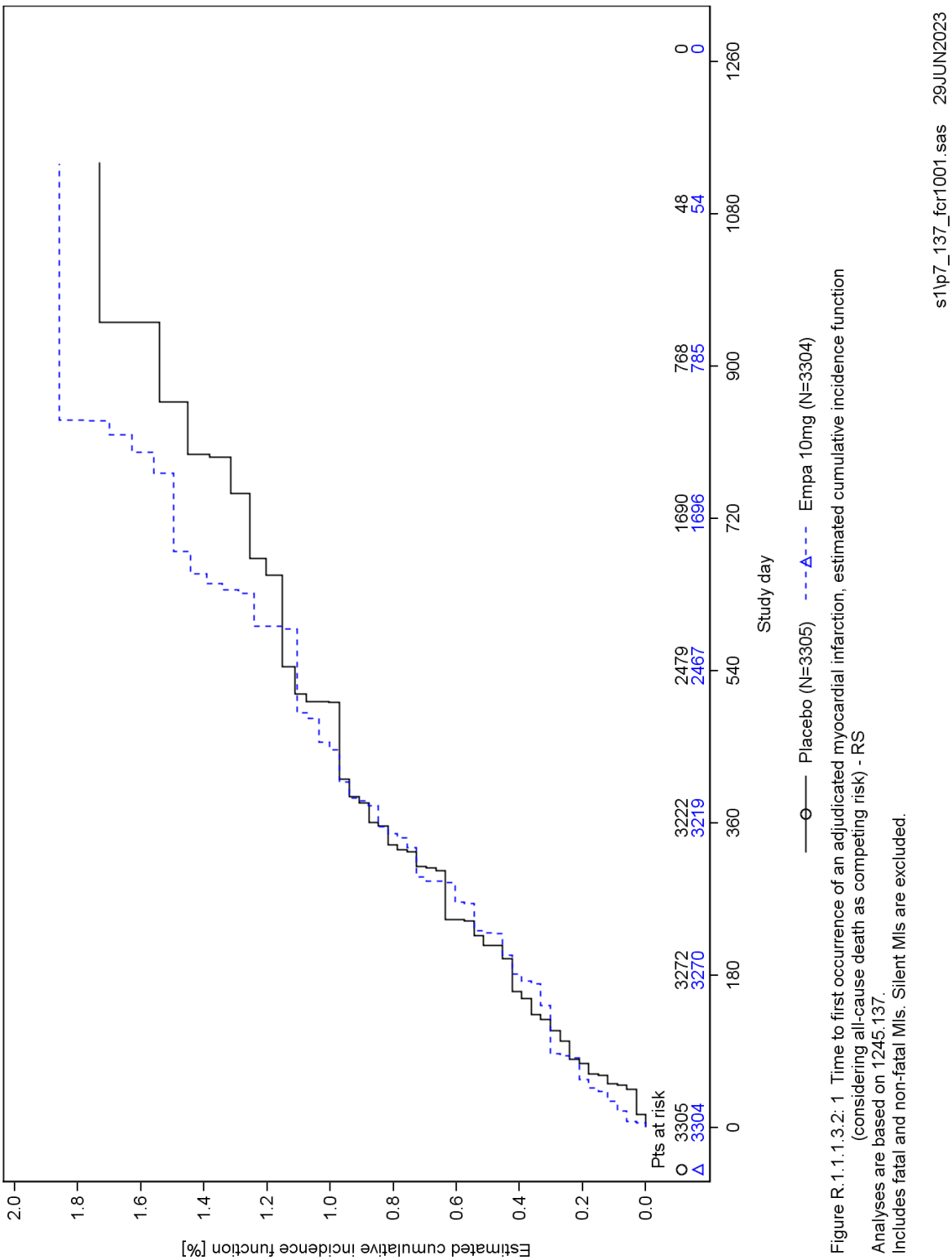


Figure R.1.1.1.3.2: 1 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.137.
Includes fatal and non-fatal MIs. Silent MIs are excluded.

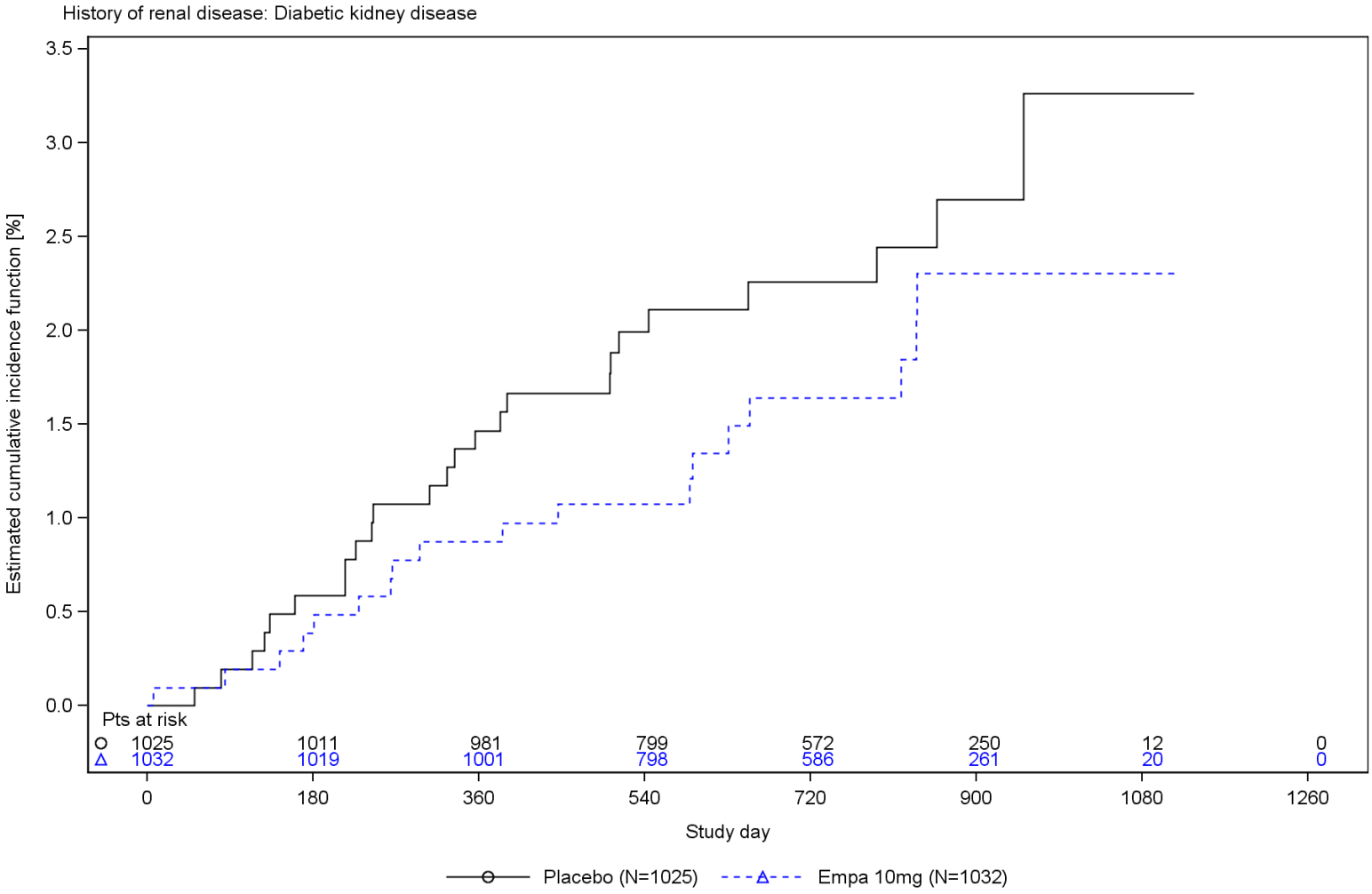


Figure R.1.1.1.3.2: 2 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: history of renal disease - RS
Analyses are based on 1245.137.
Includes fatal and non-fatal MIs. Silent MIs are excluded.

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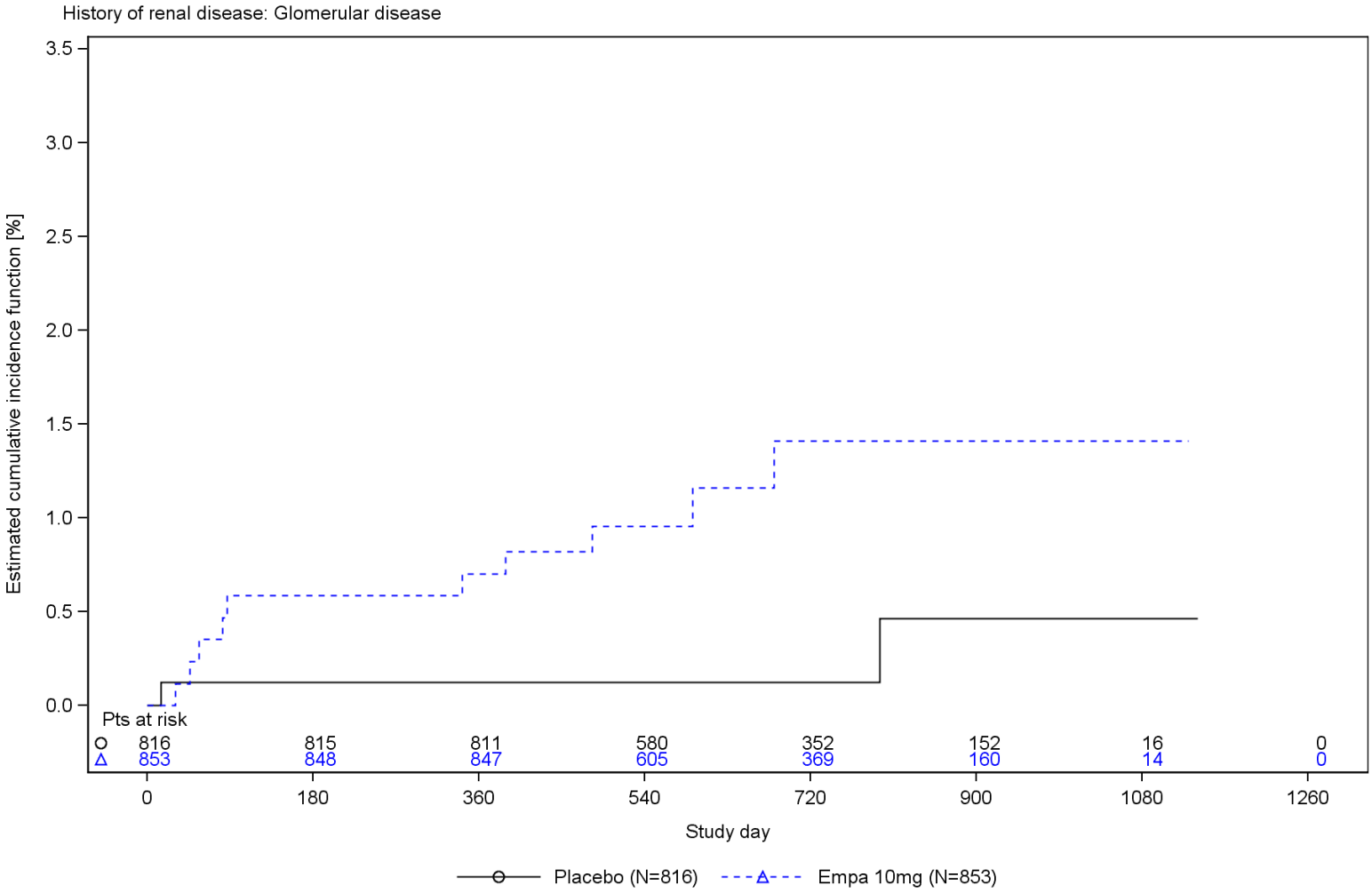


Figure R.1.1.1.3.2: 2 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: history of renal disease - RS
Analyses are based on 1245.137.
Includes fatal and non-fatal MIs. Silent MIs are excluded.

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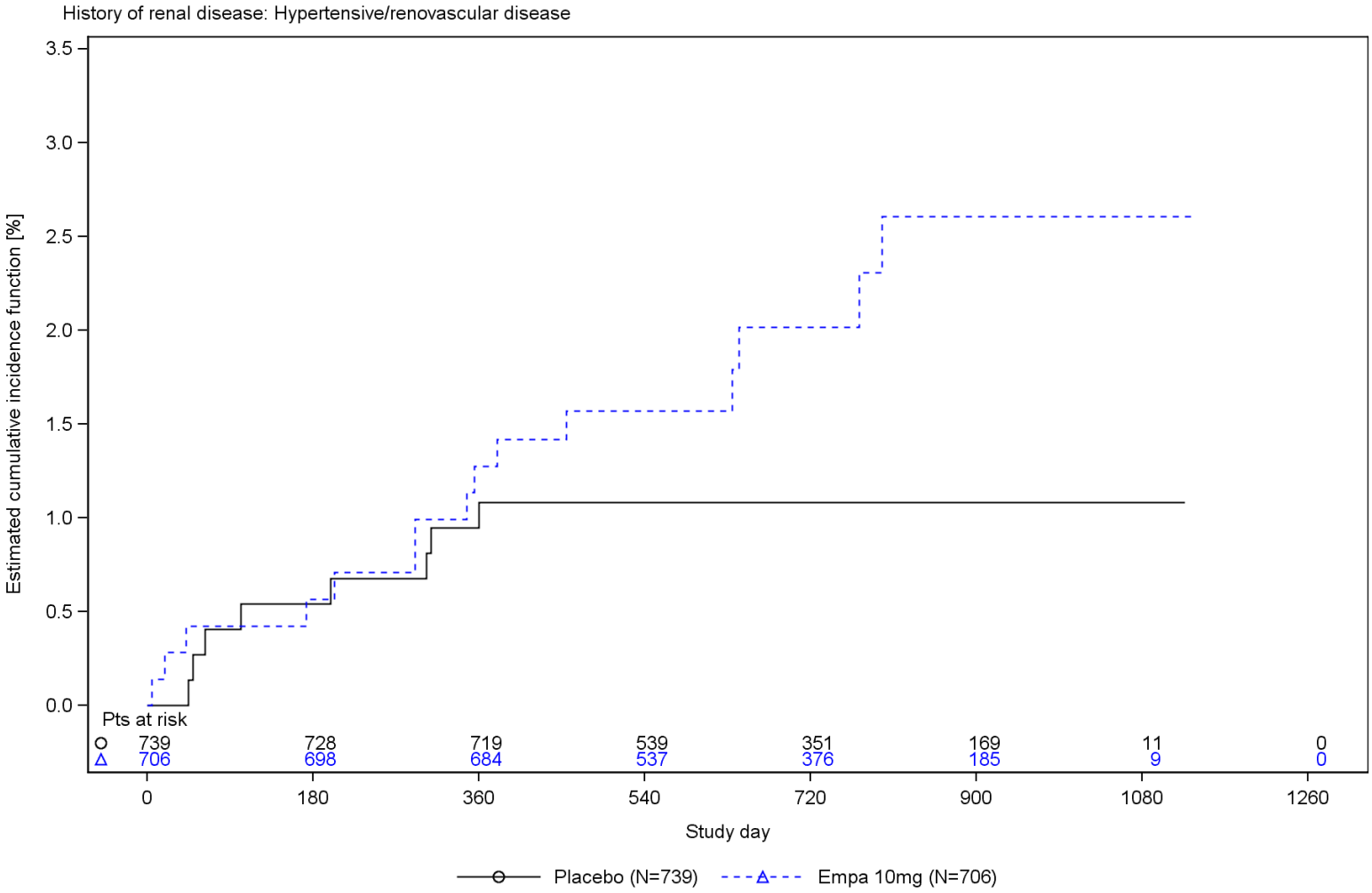


Figure R.1.1.1.3.2: 2 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: history of renal disease - RS

Analyses are based on 1245.137.

Includes fatal and non-fatal MIs. Silent MIs are excluded.

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**Figure R.1.1.1.3.2: 2**

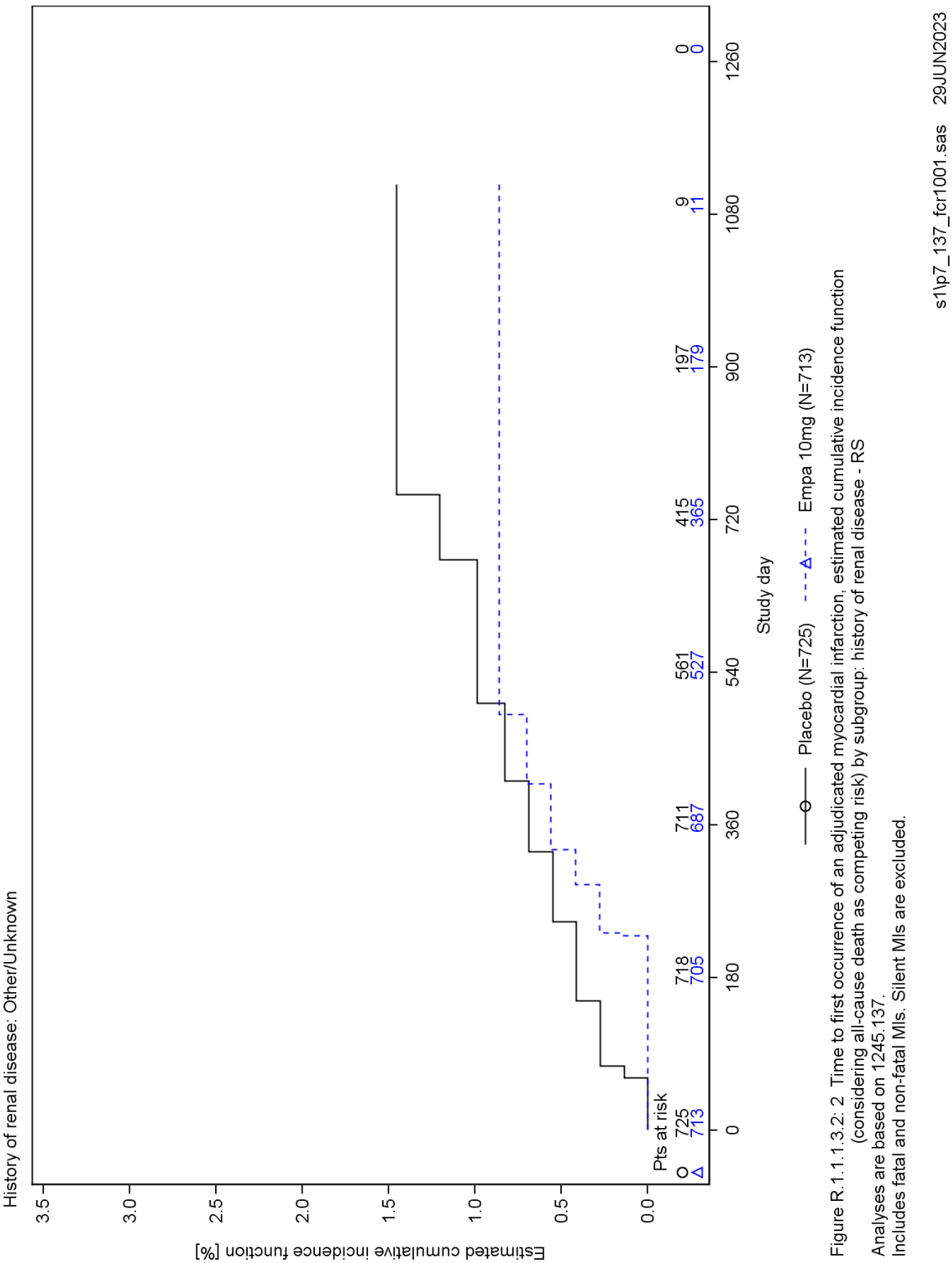


Figure R.1.1.1.3.2: 2 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: history of renal disease - RS

Analyses are based on 1245.137.
Includes fatal and non-fatal MIs. Silent MIs are excluded.

R.1.1.1.3.3 Time to first occurrence of an adjudicated stroke

Table R.1.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 49 | 1.5 | 0.76 | 3304 | 48 | 1.5 | 0.74 | 0.98 | (0.66,1.46) | 0.9307 | |
| Sex | | | | | | | | | | | | 0.0489 |
| Male | 2210 | 34 | 1.5 | 0.79 | 2207 | 41 | 1.9 | 0.95 | 1.23 | (0.78,1.94) | 0.3772 | |
| Female | 1095 | 15 | 1.4 | 0.70 | 1097 | 7 | 0.6 | 0.33 | 0.45 | (0.18,1.09) | 0.0780 | |
| Age [years] | | | | | | | | | | | | 0.2558 |
| <65 | 1501 | 16 | 1.1 | 0.55 | 1501 | 11 | 0.7 | 0.38 | 0.67 | (0.31,1.45) | 0.3126 | |
| >=65 | 1804 | 33 | 1.8 | 0.93 | 1803 | 37 | 2.1 | 1.04 | 1.13 | (0.71,1.81) | 0.5981 | |
| Region | | | | | | | | | | | | 0.9327 |
| North America | 873 | 12 | 1.4 | 0.74 | 844 | 12 | 1.4 | 0.75 | 1.04 | (0.46,2.31) | 0.9317 | |
| Europe | 1304 | 22 | 1.7 | 0.82 | 1344 | 19 | 1.4 | 0.69 | 0.85 | (0.46,1.56) | 0.5914 | |
| Japan | 308 | 4 | 1.3 | 0.62 | 304 | 4 | 1.3 | 0.64 | 1.11 | (0.28,4.45) | 0.8811 | |
| Other Asia | 820 | 11 | 1.3 | 0.74 | 812 | 13 | 1.6 | 0.88 | 1.16 | (0.52,2.58) | 0.7228 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.4638 |
| Diabetic | 1515 | 29 | 1.9 | 0.96 | 1525 | 32 | 2.1 | 1.05 | 1.10 | (0.67,1.82) | 0.7074 | |
| Non-diabetic | 1790 | 20 | 1.1 | 0.58 | 1779 | 16 | 0.9 | 0.47 | 0.81 | (0.42,1.56) | 0.5249 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2072 |
| <30 | 1961 | 24 | 1.2 | 0.64 | 1955 | 29 | 1.5 | 0.77 | 1.24 | (0.72,2.14) | 0.4311 | |
| >=30 | 1337 | 25 | 1.9 | 0.93 | 1340 | 19 | 1.4 | 0.71 | 0.74 | (0.41,1.34) | 0.3223 | |
| Prior CV disease | | | | | | | | | | | | 0.1821 |
| No | 2401 | 29 | 1.2 | 0.62 | 2443 | 23 | 0.9 | 0.48 | 0.77 | (0.45,1.34) | 0.3585 | |
| Yes | 904 | 20 | 2.2 | 1.14 | 861 | 25 | 2.9 | 1.48 | 1.34 | (0.74,2.41) | 0.3322 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0076 |
| <130 | 1208 | 22 | 1.8 | 0.94 | 1190 | 9 | 0.8 | 0.39 | 0.41 | (0.19,0.90) | 0.0256 | |
| >=130 | 2097 | 27 | 1.3 | 0.66 | 2114 | 39 | 1.8 | 0.94 | 1.44 | (0.88,2.36) | 0.1421 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4457 |
| <75 | 1286 | 19 | 1.5 | 0.75 | 1294 | 22 | 1.7 | 0.86 | 1.12 | (0.61,2.08) | 0.7088 | |
| 75 to <85 | 1033 | 11 | 1.1 | 0.54 | 1019 | 13 | 1.3 | 0.65 | 1.26 | (0.56,2.81) | 0.5775 | |
| >=85 | 986 | 19 | 1.9 | 1.01 | 991 | 13 | 1.3 | 0.69 | 0.68 | (0.33,1.37) | 0.2784 | |
| History of heart failure | | | | | | | | | | | | 0.3072 |
| No | 2970 | 45 | 1.5 | 0.78 | 2979 | 41 | 1.4 | 0.70 | 0.91 | (0.60,1.39) | 0.6669 | |
| Yes | 334 | 4 | 1.2 | 0.61 | 324 | 7 | 2.2 | 1.11 | 1.79 | (0.52,6.13) | 0.3514 | |
| History of renal disease | | | | | | | | | | | | 0.2144 |
| Diabetic kidney disease | 1025 | 19 | 1.9 | 0.93 | 1032 | 18 | 1.7 | 0.87 | 0.95 | (0.50,1.81) | 0.8689 | |
| Glomerular disease | 816 | 6 | 0.7 | 0.39 | 853 | 4 | 0.5 | 0.25 | 0.65 | (0.18,2.29) | 0.4985 | |
| Hypertensive/renovascular disease | 739 | 7 | 0.9 | 0.49 | 706 | 15 | 2.1 | 1.07 | 2.18 | (0.89,5.36) | 0.0883 | |
| Other/Unknown | 725 | 17 | 2.3 | 1.17 | 713 | 11 | 1.5 | 0.79 | 0.67 | (0.31,1.42) | 0.2948 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.7169 |
| <30 | 1151 | 17 | 1.5 | 0.76 | 1131 | 20 | 1.8 | 0.90 | 1.21 | (0.63,2.31) | 0.5685 | |
| 30 to <45 | 1461 | 22 | 1.5 | 0.76 | 1467 | 19 | 1.3 | 0.66 | 0.85 | (0.46,1.57) | 0.5963 | |
| >=45 | 693 | 10 | 1.4 | 0.76 | 706 | 9 | 1.3 | 0.66 | 0.88 | (0.36,2.18) | 0.7877 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7448 |
| Normal (<30) | 663 | 10 | 1.5 | 0.76 | 665 | 13 | 2.0 | 0.99 | 1.29 | (0.57,2.95) | 0.5445 | |
| Microalbuminuria (30 to <=300) | 937 | 13 | 1.4 | 0.71 | 927 | 11 | 1.2 | 0.60 | 0.85 | (0.38,1.89) | 0.6839 | |
| Macroalbuminuria (>300) | 1705 | 26 | 1.5 | 0.79 | 1712 | 24 | 1.4 | 0.72 | 0.93 | (0.53,1.62) | 0.7977 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7629 |
| Low, moderate or high | 833 | 13 | 1.6 | 0.80 | 839 | 14 | 1.7 | 0.86 | 1.08 | (0.51,2.30) | 0.8446 | |
| Very high | 2472 | 36 | 1.5 | 0.75 | 2465 | 34 | 1.4 | 0.70 | 0.94 | (0.59,1.50) | 0.7975 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.5394 |
| No | 508 | 11 | 2.2 | 1.17 | 473 | 8 | 1.7 | 0.90 | 0.76 | (0.31,1.90) | 0.5606 | |
| Yes | 2797 | 38 | 1.4 | 0.69 | 2831 | 40 | 1.4 | 0.72 | 1.05 | (0.67,1.63) | 0.8358 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.2093 |
| No | 1940 | 31 | 1.6 | 0.83 | 1908 | 23 | 1.2 | 0.62 | 0.78 | (0.46,1.34) | 0.3737 | |
| Yes | 1365 | 18 | 1.3 | 0.67 | 1396 | 25 | 1.8 | 0.90 | 1.32 | (0.72,2.42) | 0.3731 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3215 |
| No | 1852 | 24 | 1.3 | 0.68 | 1942 | 29 | 1.5 | 0.78 | 1.18 | (0.69,2.03) | 0.5511 | |
| Yes | 1453 | 25 | 1.7 | 0.86 | 1362 | 19 | 1.4 | 0.69 | 0.78 | (0.43,1.42) | 0.4243 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.3.3: 1**

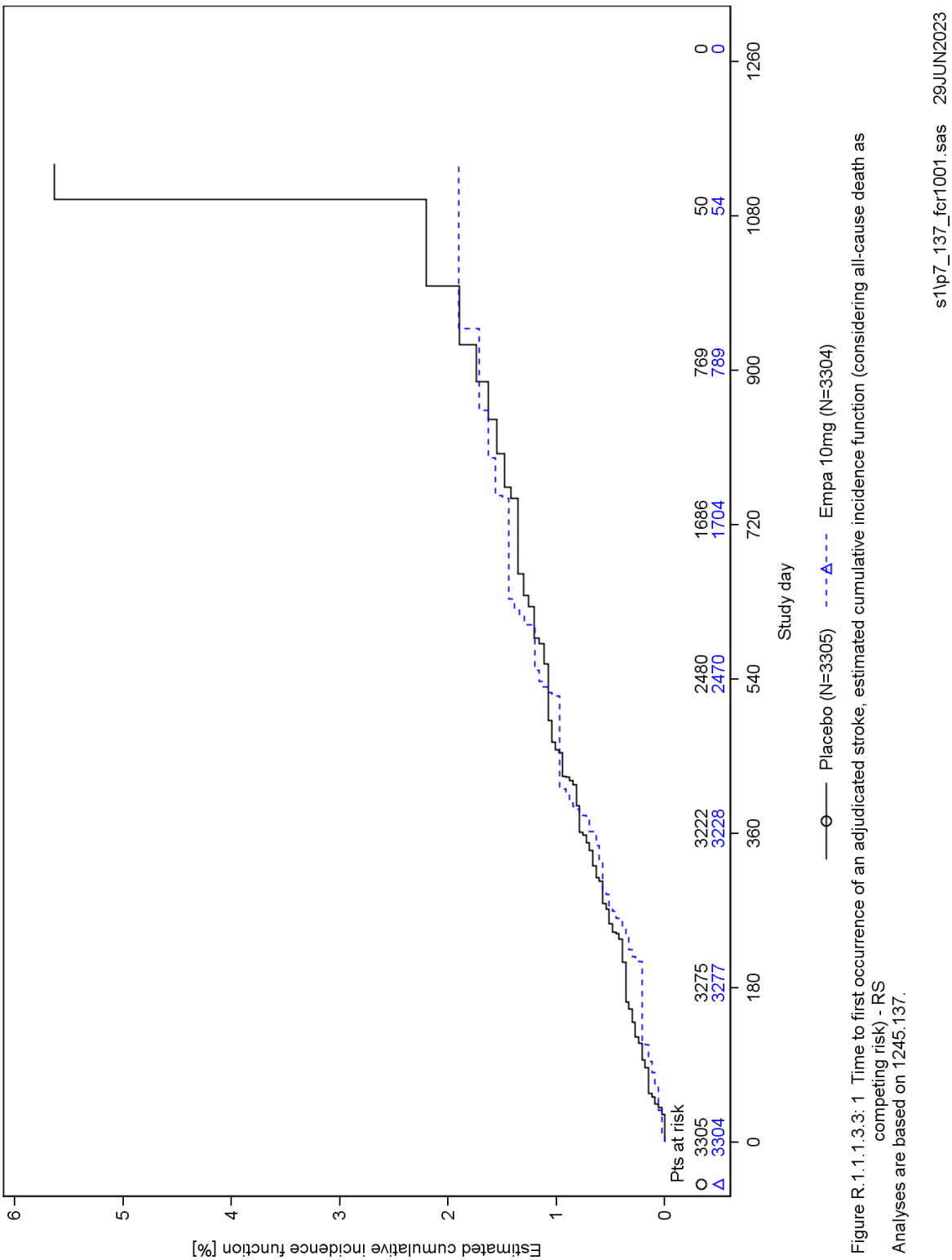


Figure R.1.1.1.3.3: 1 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.3.3: 2**

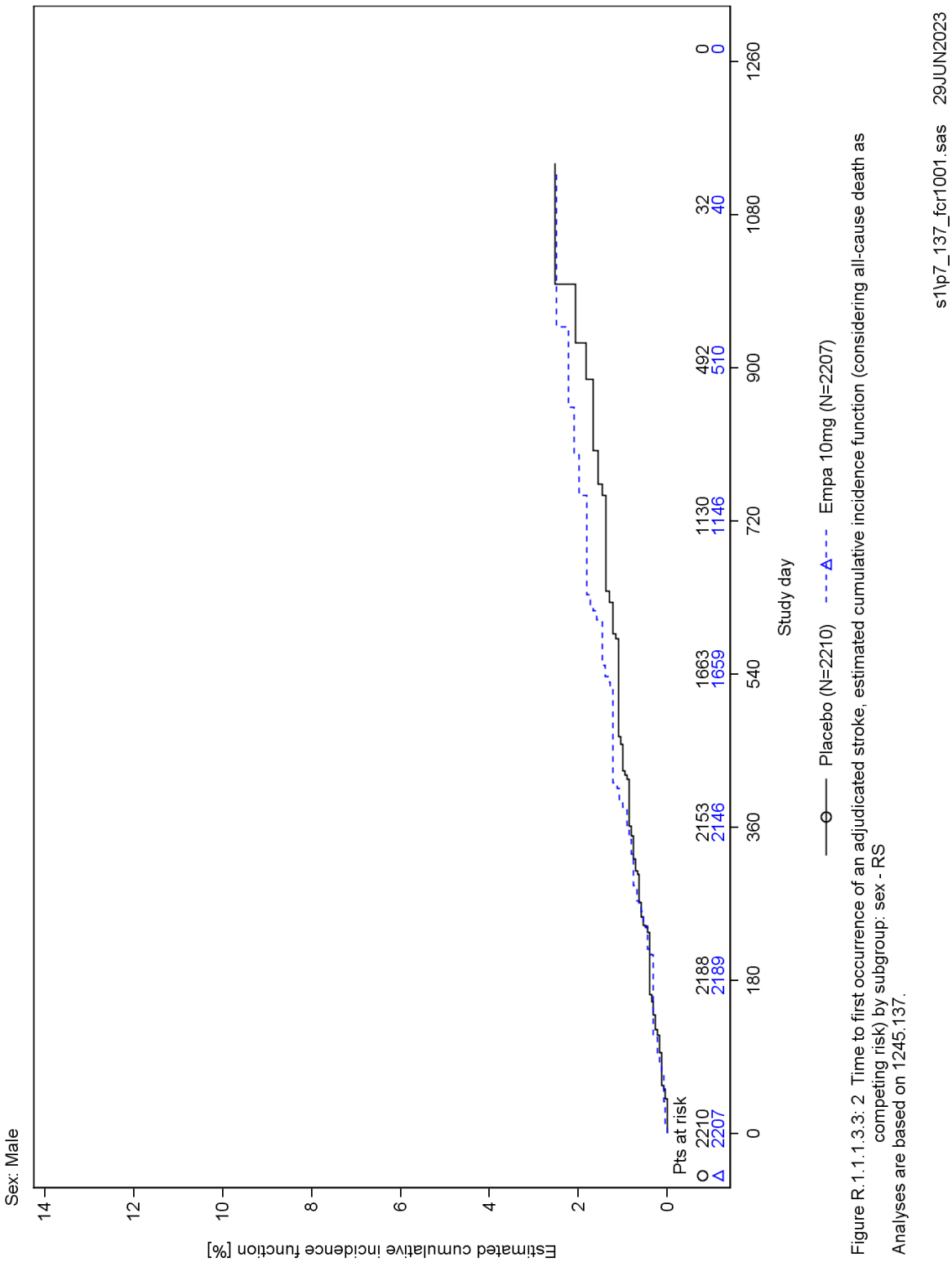


Figure R.1.1.1.3.3: 2 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: sex - RS

Analyses are based on 1245.137.

**Figure R.1.1.1.3.3: 2**

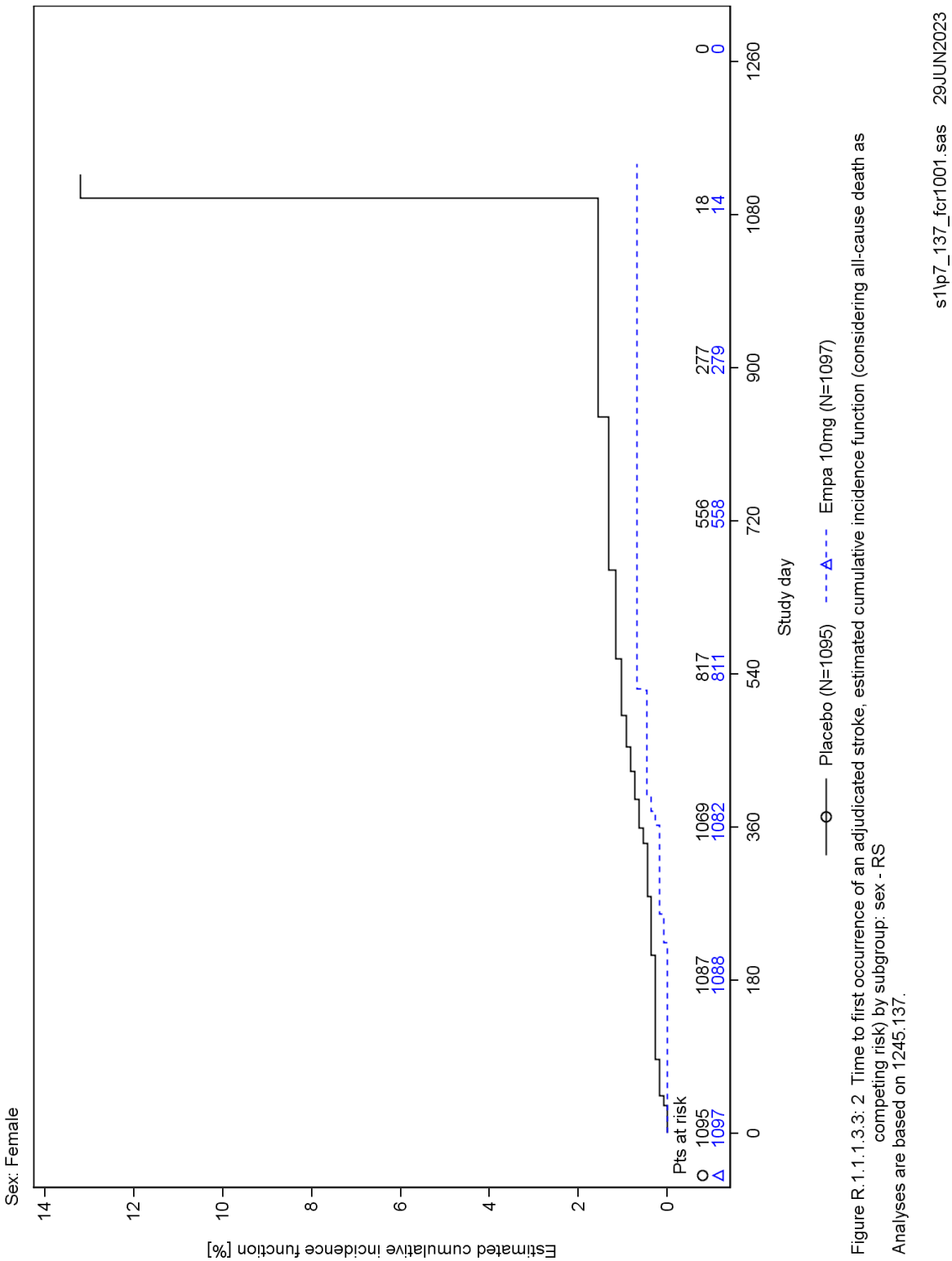


Figure R.1.1.1.3.3: 2 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: sex - RS

Analyses are based on 1245.137.

**Figure R.1.1.1.3.3: 3**

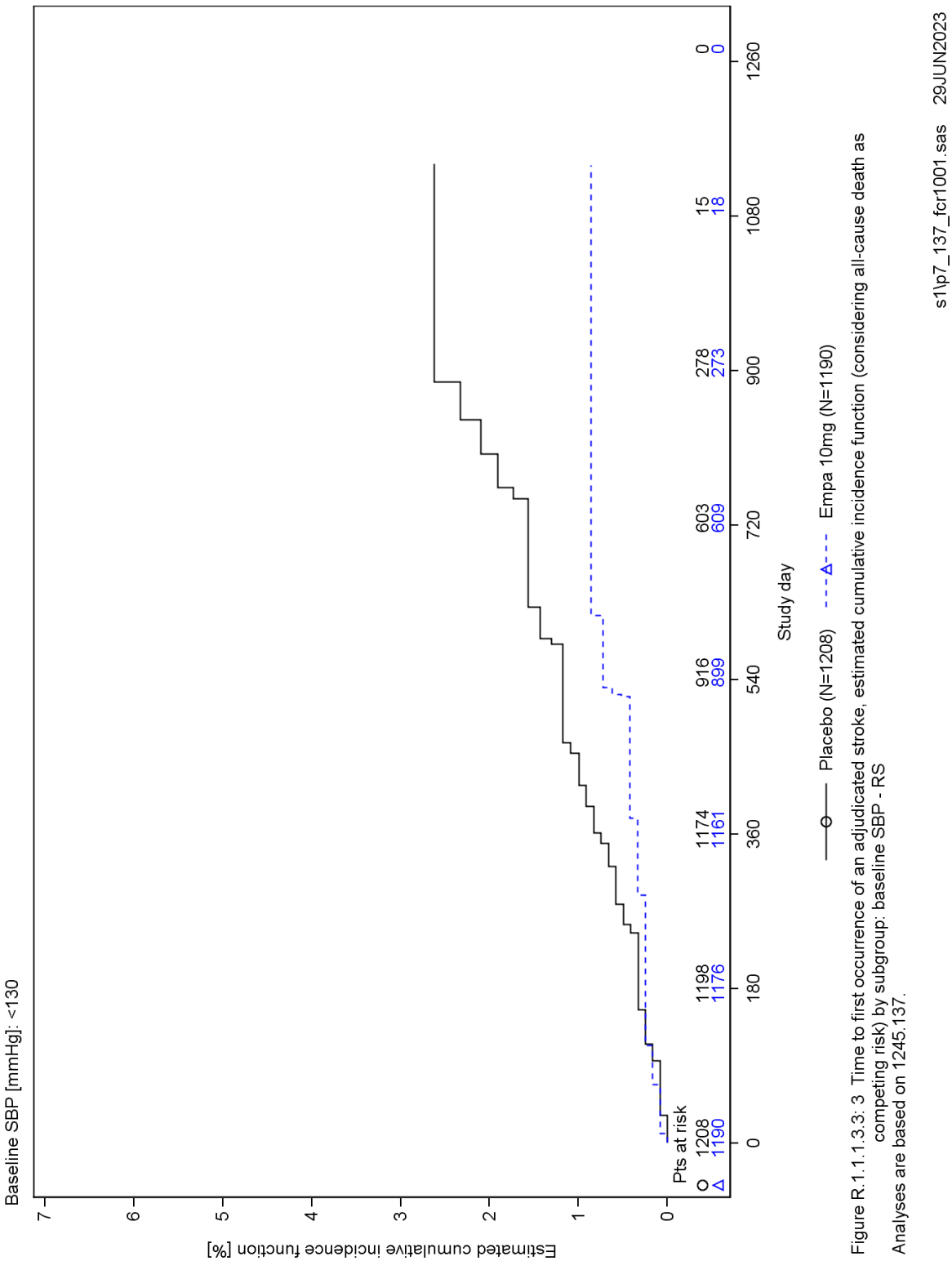


Figure R.1.1.1.3.3: 3 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on 1245.137.

**Figure R.1.1.1.3.3: 3**

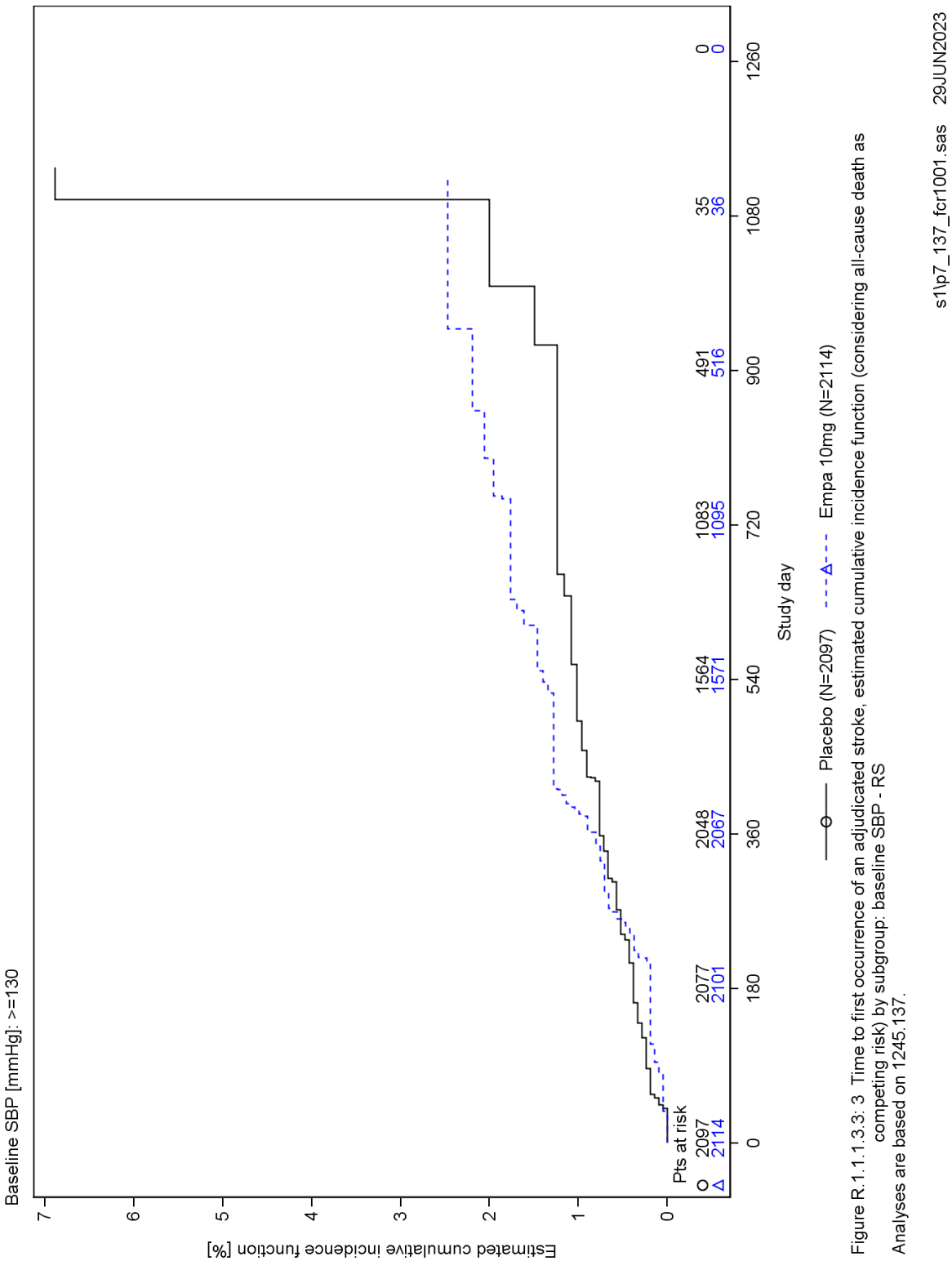


Figure R.1.1.1.3.3: 3 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on 1245.137.

R.1.1.1.3.4 Time to first adjudicated hospitalization for heart failure

Table R.1.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 107 | 3.2 | 1.67 | 3304 | 88 | 2.7 | 1.37 | 0.80 | (0.60,1.06) | 0.1263 | |
| Sex | | | | | | | | | | | | 0.9869 |
| Male | 2210 | 82 | 3.7 | 1.92 | 2207 | 67 | 3.0 | 1.56 | 0.80 | (0.58,1.11) | 0.1848 | |
| Female | 1095 | 25 | 2.3 | 1.18 | 1097 | 21 | 1.9 | 0.98 | 0.80 | (0.45,1.43) | 0.4491 | |
| Age [years] | | | | | | | | | | | | 0.2809 |
| <65 | 1501 | 18 | 1.2 | 0.62 | 1501 | 21 | 1.4 | 0.72 | 1.11 | (0.59,2.08) | 0.7519 | |
| >=65 | 1804 | 89 | 4.9 | 2.54 | 1803 | 67 | 3.7 | 1.90 | 0.75 | (0.55,1.03) | 0.0767 | |
| Region | | | | | | | | | | | | 0.5861 |
| North America | 873 | 26 | 3.0 | 1.61 | 844 | 24 | 2.8 | 1.51 | 0.92 | (0.53,1.61) | 0.7757 | |
| Europe | 1304 | 58 | 4.4 | 2.18 | 1344 | 49 | 3.6 | 1.79 | 0.80 | (0.54,1.17) | 0.2409 | |
| Japan | 308 | 10 | 3.2 | 1.56 | 304 | 3 | 1.0 | 0.48 | 0.35 | (0.10,1.27) | 0.1100 | |
| Other Asia | 820 | 13 | 1.6 | 0.88 | 812 | 12 | 1.5 | 0.81 | 0.91 | (0.41,1.99) | 0.8109 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.7321 |
| Diabetic | 1515 | 80 | 5.3 | 2.69 | 1525 | 65 | 4.3 | 2.15 | 0.78 | (0.56,1.08) | 0.1322 | |
| Non-diabetic | 1790 | 27 | 1.5 | 0.79 | 1779 | 23 | 1.3 | 0.67 | 0.87 | (0.50,1.52) | 0.6243 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.8532 |
| <30 | 1961 | 46 | 2.3 | 1.23 | 1955 | 38 | 1.9 | 1.01 | 0.83 | (0.54,1.28) | 0.4082 | |
| >=30 | 1337 | 60 | 4.5 | 2.25 | 1340 | 50 | 3.7 | 1.89 | 0.79 | (0.54,1.15) | 0.2195 | |
| Prior CV disease | | | | | | | | | | | | 0.5681 |
| No | 2401 | 34 | 1.4 | 0.73 | 2443 | 33 | 1.4 | 0.69 | 0.93 | (0.57,1.49) | 0.7513 | |
| Yes | 904 | 73 | 8.1 | 4.26 | 861 | 55 | 6.4 | 3.31 | 0.78 | (0.55,1.11) | 0.1615 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8214 |
| <130 | 1208 | 35 | 2.9 | 1.49 | 1190 | 28 | 2.4 | 1.21 | 0.84 | (0.51,1.39) | 0.4995 | |
| >=130 | 2097 | 72 | 3.4 | 1.77 | 2114 | 60 | 2.8 | 1.46 | 0.79 | (0.56,1.11) | 0.1688 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3194 |
| <75 | 1286 | 69 | 5.4 | 2.78 | 1294 | 51 | 3.9 | 2.00 | 0.70 | (0.49,1.01) | 0.0574 | |
| 75 to <85 | 1033 | 24 | 2.3 | 1.18 | 1019 | 27 | 2.6 | 1.35 | 1.15 | (0.66,2.00) | 0.6194 | |
| >=85 | 986 | 14 | 1.4 | 0.74 | 991 | 10 | 1.0 | 0.53 | 0.69 | (0.30,1.54) | 0.3618 | |
| History of heart failure | | | | | | | | | | | | 0.6994 |
| No | 2970 | 69 | 2.3 | 1.20 | 2979 | 59 | 2.0 | 1.02 | 0.84 | (0.59,1.19) | 0.3170 | |
| Yes | 334 | 38 | 11.4 | 6.01 | 324 | 29 | 9.0 | 4.72 | 0.74 | (0.46,1.21) | 0.2328 | |
| History of renal disease | | | | | | | | | | | | 0.6772 |
| Diabetic kidney disease | 1025 | 51 | 5.0 | 2.54 | 1032 | 50 | 4.8 | 2.46 | 0.93 | (0.63,1.38) | 0.7335 | |
| Glomerular disease | 816 | 4 | 0.5 | 0.26 | 853 | 4 | 0.5 | 0.25 | 0.96 | (0.24,3.85) | 0.9565 | |
| Hypertensive/renovascular disease | 739 | 27 | 3.7 | 1.92 | 706 | 19 | 2.7 | 1.36 | 0.70 | (0.39,1.26) | 0.2338 | |
| Other/Unknown | 725 | 25 | 3.4 | 1.73 | 713 | 15 | 2.1 | 1.08 | 0.61 | (0.32,1.17) | 0.1358 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6655 |
| <30 | 1151 | 48 | 4.2 | 2.16 | 1131 | 45 | 4.0 | 2.05 | 0.93 | (0.62,1.39) | 0.7180 | |
| 30 to <45 | 1461 | 52 | 3.6 | 1.82 | 1467 | 38 | 2.6 | 1.32 | 0.72 | (0.47,1.09) | 0.1177 | |
| >=45 | 693 | 7 | 1.0 | 0.53 | 706 | 5 | 0.7 | 0.37 | 0.71 | (0.22,2.23) | 0.5538 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7199 |
| Normal (<30) | 663 | 21 | 3.2 | 1.60 | 665 | 17 | 2.6 | 1.30 | 0.84 | (0.44,1.59) | 0.5880 | |
| Microalbuminuria (30 to <=300) | 937 | 32 | 3.4 | 1.76 | 927 | 30 | 3.2 | 1.66 | 0.92 | (0.56,1.52) | 0.7462 | |
| Macroalbuminuria (>300) | 1705 | 54 | 3.2 | 1.65 | 1712 | 41 | 2.4 | 1.24 | 0.71 | (0.47,1.07) | 0.0988 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.6760 |
| Low, moderate or high | 833 | 19 | 2.3 | 1.17 | 839 | 13 | 1.5 | 0.80 | 0.70 | (0.35,1.42) | 0.3246 | |
| Very high | 2472 | 88 | 3.6 | 1.84 | 2465 | 75 | 3.0 | 1.56 | 0.83 | (0.61,1.13) | 0.2263 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.7715 |
| No | 508 | 20 | 3.9 | 2.14 | 473 | 14 | 3.0 | 1.58 | 0.73 | (0.37,1.45) | 0.3730 | |
| Yes | 2797 | 87 | 3.1 | 1.59 | 2831 | 74 | 2.6 | 1.33 | 0.82 | (0.60,1.12) | 0.2075 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9894 |
| No | 1940 | 34 | 1.8 | 0.91 | 1908 | 26 | 1.4 | 0.70 | 0.79 | (0.48,1.32) | 0.3738 | |
| Yes | 1365 | 73 | 5.3 | 2.76 | 1396 | 62 | 4.4 | 2.27 | 0.79 | (0.56,1.11) | 0.1727 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.7903 |
| No | 1852 | 20 | 1.1 | 0.56 | 1942 | 19 | 1.0 | 0.51 | 0.89 | (0.48,1.67) | 0.7224 | |
| Yes | 1453 | 87 | 6.0 | 3.05 | 1362 | 69 | 5.1 | 2.56 | 0.81 | (0.59,1.11) | 0.1952 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.3.4: 1**

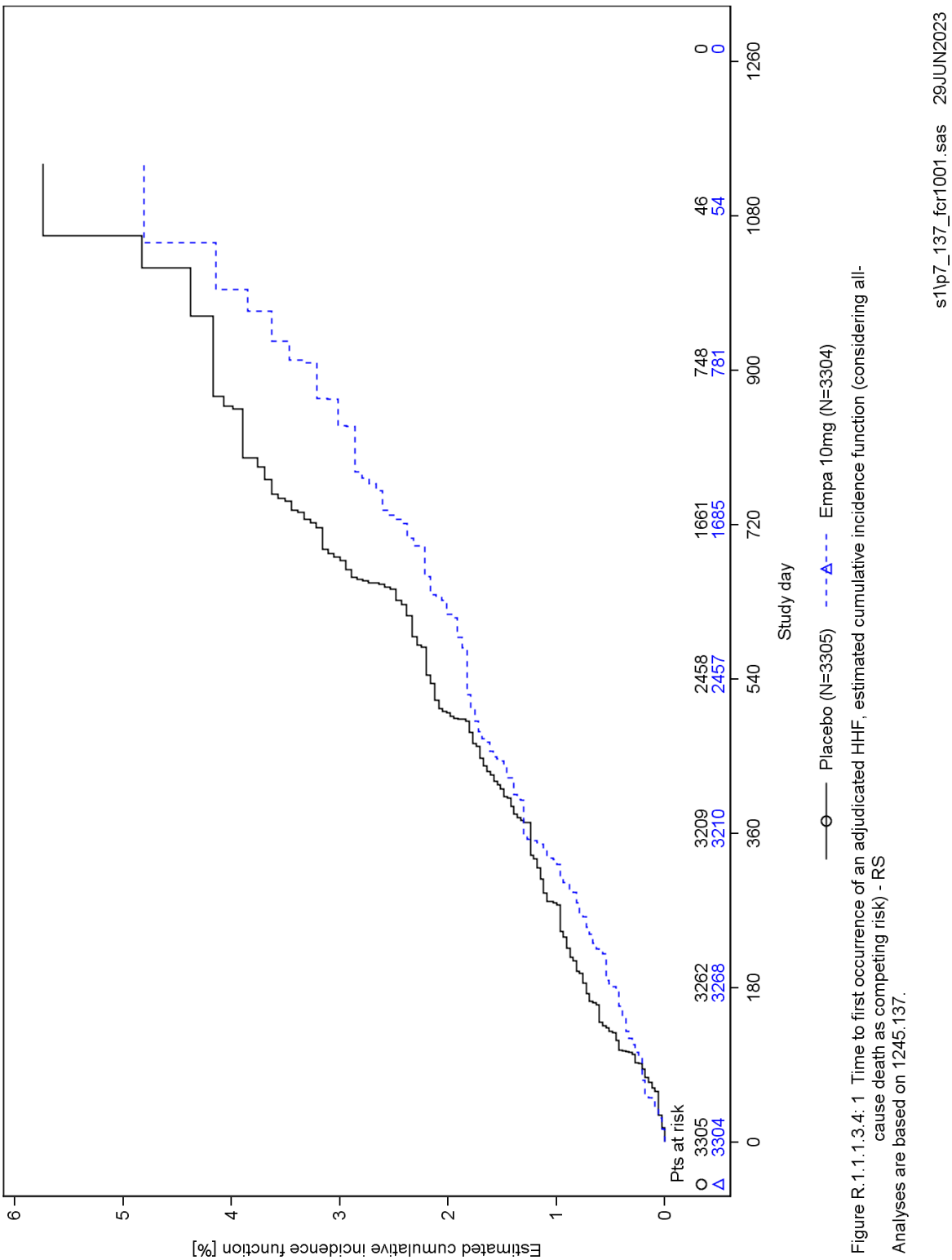


Figure R.1.1.1.3.4: 1 Time to first occurrence of an adjudicated HHF, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.137.

R.1.1.1.3.5 Time to occurrence of adjudicated hospitalization for heart failure (first and recurrent)

Table R.1.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 107 | 3.2 | 154 | 2.37 | 3304 | 88 | 2.7 | 118 | 1.82 | 0.77 | (0.58,1.02) | 0.0669 | |
| Sex | | | | | | | | | | | | | | 0.2890 |
| Male | 2210 | 82 | 3.7 | 116 | 2.67 | 2207 | 67 | 3.0 | 94 | 2.17 | 0.84 | (0.61,1.16) | 0.2951 | |
| Female | 1095 | 25 | 2.3 | 38 | 1.77 | 1097 | 21 | 1.9 | 24 | 1.11 | 0.59 | (0.33,1.04) | 0.0695 | |
| Age [years] | | | | | | | | | | | | | | 0.0143 |
| <65 | 1501 | 18 | 1.2 | 22 | 0.76 | 1501 | 21 | 1.4 | 32 | 1.10 | 1.46 | (0.81,2.62) | 0.2056 | |
| >=65 | 1804 | 89 | 4.9 | 132 | 3.70 | 1803 | 67 | 3.7 | 86 | 2.40 | 0.63 | (0.46,0.87) | 0.0057 | |
| Region | | | | | | | | | | | | | | NC. |
| North America | 873 | 26 | 3.0 | 33 | 2.02 | 844 | 24 | 2.8 | 30 | 1.87 | NC. | | | |
| Europe | 1304 | 58 | 4.4 | 88 | 3.25 | 1344 | 49 | 3.6 | 66 | 2.38 | NC. | | | |
| Japan | 308 | 10 | 3.2 | 11 | 1.70 | 304 | 3 | 1.0 | 4 | 0.64 | NC. | | | |
| Other Asia | 820 | 13 | 1.6 | 22 | 1.47 | 812 | 12 | 1.5 | 18 | 1.21 | NC. | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8877 |
| Diabetic | 1515 | 80 | 5.3 | 111 | 3.66 | 1525 | 65 | 4.3 | 87 | 2.84 | 0.74 | (0.53,1.04) | 0.0821 | |
| Non-diabetic | 1790 | 27 | 1.5 | 43 | 1.25 | 1779 | 23 | 1.3 | 31 | 0.90 | 0.78 | (0.47,1.29) | 0.3290 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5423 |
| <30 | 1961 | 46 | 2.3 | 66 | 1.75 | 1955 | 38 | 1.9 | 52 | 1.37 | 0.84 | (0.56,1.27) | 0.4060 | |
| >=30 | 1337 | 60 | 4.5 | 87 | 3.22 | 1340 | 50 | 3.7 | 66 | 2.45 | 0.71 | (0.48,1.03) | 0.0728 | |
| Prior CV disease | | | | | | | | | | | | | | 0.3162 |
| No | 2401 | 34 | 1.4 | 42 | 0.89 | 2443 | 33 | 1.4 | 43 | 0.90 | 0.96 | (0.61,1.52) | 0.8744 | |
| Yes | 904 | 73 | 8.1 | 112 | 6.32 | 861 | 55 | 6.4 | 75 | 4.41 | 0.72 | (0.50,1.03) | 0.0725 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9208 |
| <130 | 1208 | 35 | 2.9 | 47 | 1.99 | 1190 | 28 | 2.4 | 35 | 1.51 | 0.78 | (0.47,1.30) | 0.3370 | |
| >=130 | 2097 | 72 | 3.4 | 107 | 2.60 | 2114 | 60 | 2.8 | 83 | 1.99 | 0.76 | (0.54,1.06) | 0.1078 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, local screening eGFR (CKD-EPI), log(local screening UACR), subgroup, screening diabetes status (2 cat.), sex, region, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.
NC. = Not calculated.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1784 |
| <75 | 1286 | 69 | 5.4 | 102 | 4.02 | 1294 | 51 | 3.9 | 68 | 2.63 | 0.66 | (0.45,0.95) | 0.0238 | |
| 75 to <85 | 1033 | 24 | 2.3 | 30 | 1.46 | 1019 | 27 | 2.6 | 35 | 1.74 | 1.20 | (0.69,2.07) | 0.5183 | |
| >=85 | 986 | 14 | 1.4 | 22 | 1.16 | 991 | 10 | 1.0 | 15 | 0.79 | 0.65 | (0.32,1.34) | 0.2442 | |
| History of heart failure | | | | | | | | | | | | | | 0.9507 |
| No | 2970 | 69 | 2.3 | 94 | 1.61 | 2979 | 59 | 2.0 | 76 | 1.30 | 0.79 | (0.57,1.10) | 0.1564 | |
| Yes | 334 | 38 | 11.4 | 60 | 9.07 | 324 | 29 | 9.0 | 42 | 6.61 | 0.77 | (0.46,1.30) | 0.3307 | |
| History of renal disease | | | | | | | | | | | | | | NC. |
| Diabetic kidney disease | 1025 | 51 | 5.0 | 68 | 3.32 | 1032 | 50 | 4.8 | 68 | 3.28 | NC. | | | |
| Glomerular disease | 816 | 4 | 0.5 | 8 | 0.52 | 853 | 4 | 0.5 | 5 | 0.31 | NC. | | | |
| Hypertensive/renovascular disease | 739 | 27 | 3.7 | 33 | 2.31 | 706 | 19 | 2.7 | 27 | 1.92 | NC. | | | |
| Other/Unknown | 725 | 25 | 3.4 | 45 | 3.08 | 713 | 15 | 2.1 | 18 | 1.29 | NC. | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5560 |
| <30 | 1151 | 48 | 4.2 | 71 | 3.14 | 1131 | 45 | 4.0 | 60 | 2.68 | 0.85 | (0.57,1.27) | 0.4399 | |
| 30 to <45 | 1461 | 52 | 3.6 | 72 | 2.48 | 1467 | 38 | 2.6 | 48 | 1.66 | 0.64 | (0.43,0.97) | 0.0363 | |
| >=45 | 693 | 7 | 1.0 | 11 | 0.83 | 706 | 5 | 0.7 | 10 | 0.73 | 0.95 | (0.38,2.36) | 0.9086 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6727 |
| Normal (<30) | 663 | 21 | 3.2 | 31 | 2.33 | 665 | 17 | 2.6 | 19 | 1.44 | 0.65 | (0.35,1.23) | 0.1868 | |
| Microalbuminuria (30 to <=300) | 937 | 32 | 3.4 | 44 | 2.38 | 927 | 30 | 3.2 | 41 | 2.24 | 0.90 | (0.55,1.48) | 0.6907 | |
| Macroalbuminuria (>300) | 1705 | 54 | 3.2 | 79 | 2.39 | 1712 | 41 | 2.4 | 58 | 1.73 | 0.72 | (0.48,1.06) | 0.0977 | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9984 |
| Low, moderate or high | 833 | 19 | 2.3 | 27 | 1.65 | 839 | 13 | 1.5 | 18 | 1.10 | 0.75 | (0.39,1.45) | 0.3962 | |
| Very high | 2472 | 88 | 3.6 | 127 | 2.62 | 2465 | 75 | 3.0 | 100 | 2.06 | 0.75 | (0.56,1.02) | 0.0666 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, local screening eGFR (CKD-EPI), log(local screening UACR), subgroup, screening diabetes status (2 cat.), sex, region, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.
NC. = Not calculated.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | | | 0.2292 |
| No | 508 | 20 | 3.9 | 33 | 3.47 | 473 | 14 | 3.0 | 17 | 1.91 | 0.53 | (0.27,1.03) | 0.0608 | |
| Yes | 2797 | 87 | 3.1 | 121 | 2.19 | 2831 | 74 | 2.6 | 101 | 1.80 | 0.83 | (0.61,1.12) | 0.2130 | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3796 |
| No | 1940 | 34 | 1.8 | 43 | 1.14 | 1908 | 26 | 1.4 | 35 | 0.94 | 0.90 | (0.55,1.46) | 0.6569 | |
| Yes | 1365 | 73 | 5.3 | 111 | 4.09 | 1396 | 62 | 4.4 | 83 | 2.98 | 0.69 | (0.49,0.97) | 0.0307 | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3465 |
| No | 1852 | 20 | 1.1 | 24 | 0.67 | 1942 | 19 | 1.0 | 25 | 0.67 | 1.02 | (0.56,1.84) | 0.9495 | |
| Yes | 1453 | 87 | 6.0 | 130 | 4.45 | 1362 | 69 | 5.1 | 93 | 3.38 | 0.74 | (0.53,1.02) | 0.0635 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, local screening eGFR (CKD-EPI), log(local screening UACR), subgroup, screening diabetes status (2 cat.), sex, region, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.
NC. = Not calculated.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.3.5: 1**

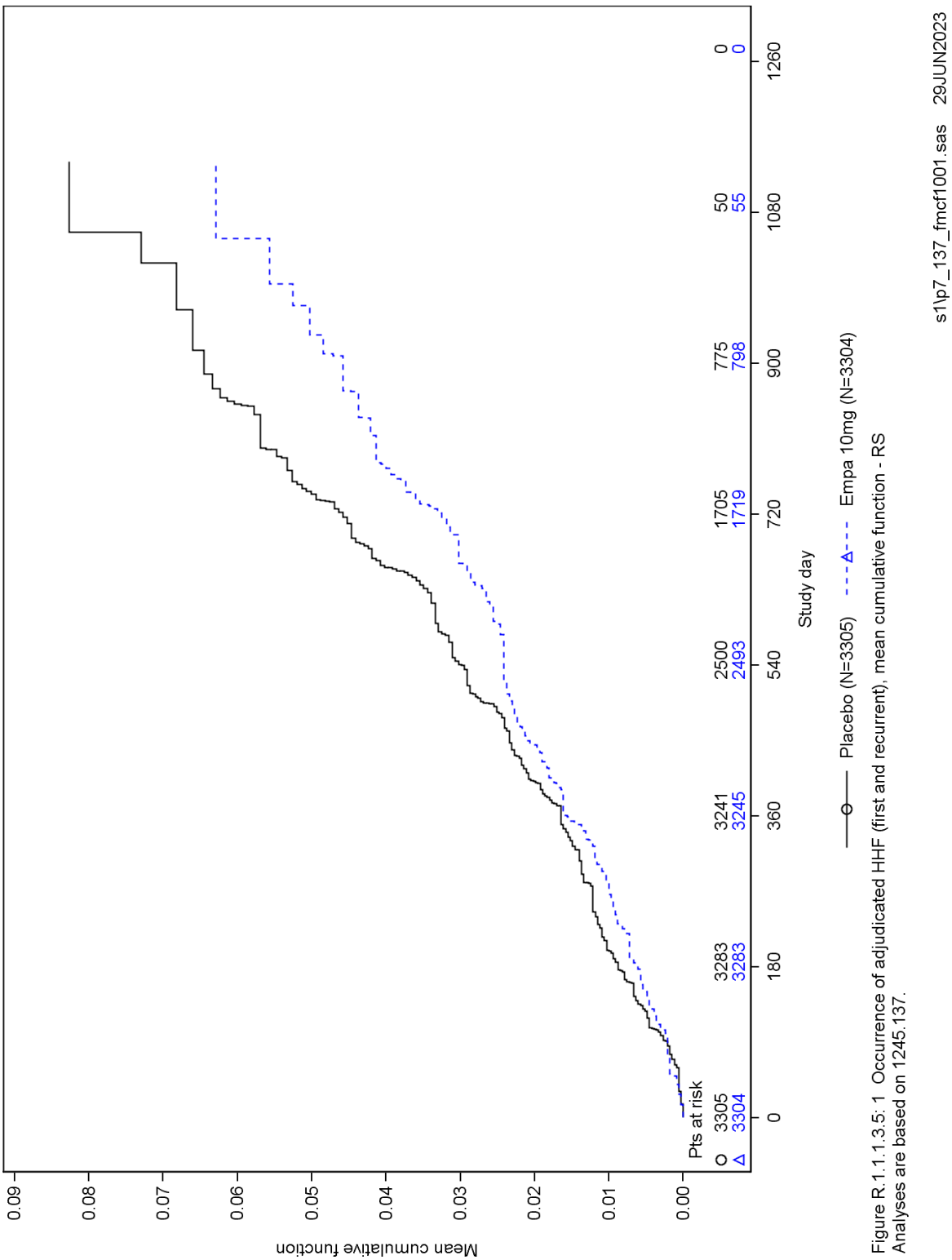


Figure R.1.1.1.3.5: 1 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.3.5: 2**

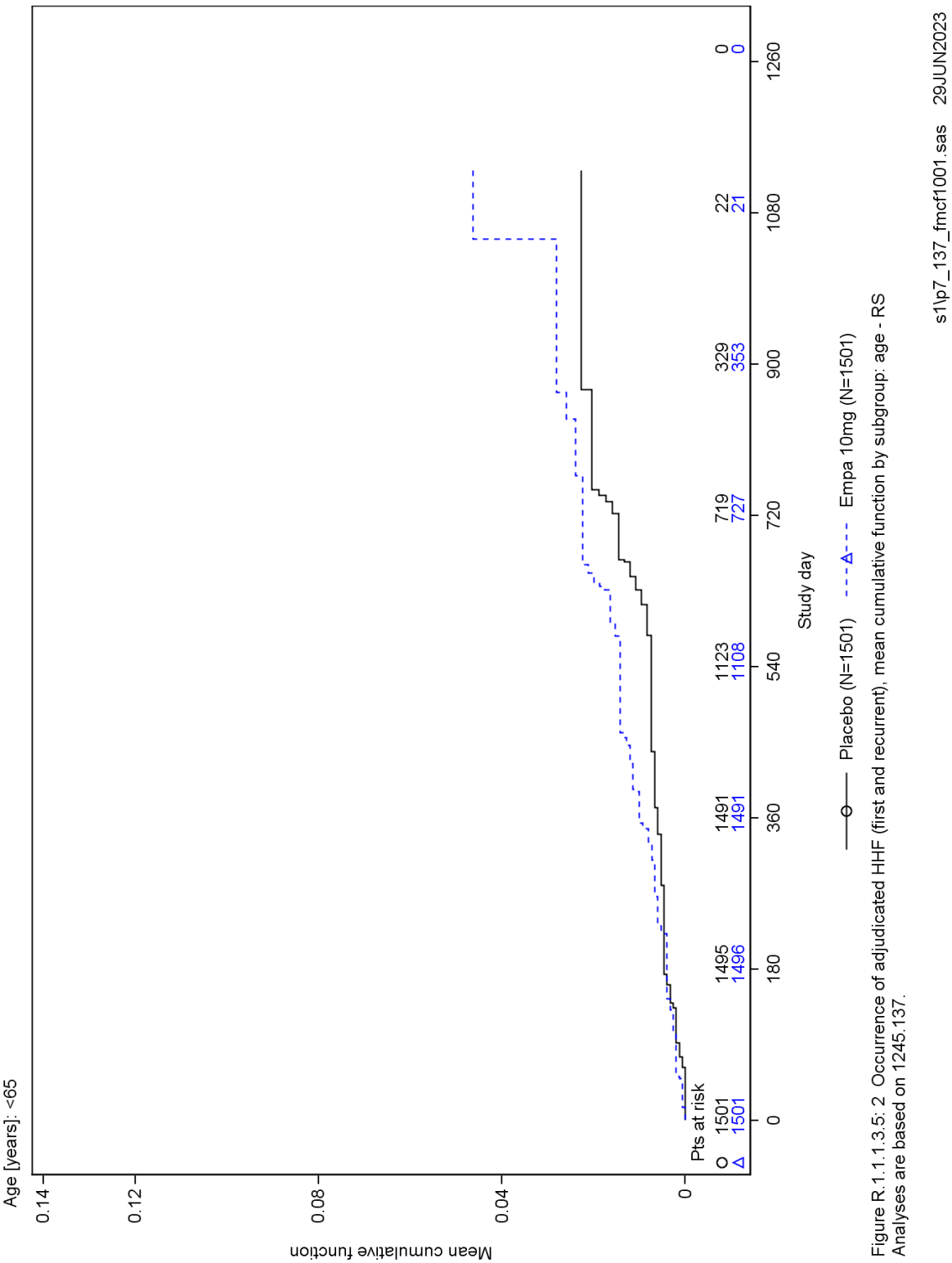


Figure R.1.1.1.3.5: 2 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: age - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.3.5: 2**

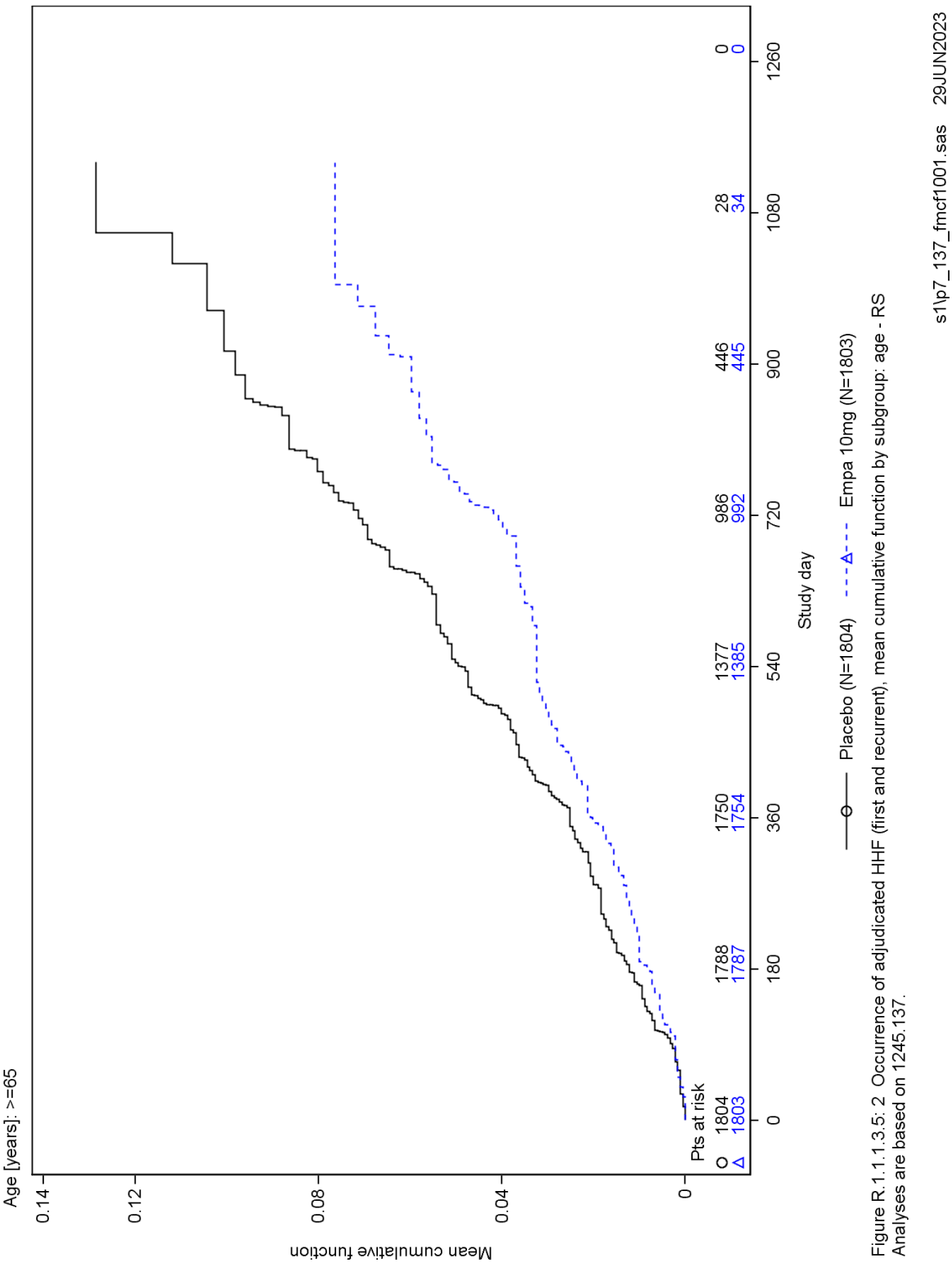


Figure R.1.1.1.3.5: 2 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: age - RS
Analyses are based on 1245.137.

R.1.1.1.3.6 Time to first occurrence of all-cause hospitalization

Table R.1.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 1035 | 31.3 | 19.13 | 3304 | 960 | 29.1 | 17.50 | 0.91 | (0.83,0.99) | 0.0328 | |
| Sex | | | | | | | | | | | | 0.0873 |
| Male | 2210 | 704 | 31.9 | 19.55 | 2207 | 676 | 30.6 | 18.63 | 0.96 | (0.86,1.06) | 0.4107 | |
| Female | 1095 | 331 | 30.2 | 18.29 | 1097 | 284 | 25.9 | 15.30 | 0.81 | (0.69,0.95) | 0.0092 | |
| Age [years] | | | | | | | | | | | | 0.0363 |
| <65 | 1501 | 332 | 22.1 | 12.98 | 1501 | 345 | 23.0 | 13.57 | 1.04 | (0.89,1.21) | 0.6316 | |
| >=65 | 1804 | 703 | 39.0 | 24.65 | 1803 | 615 | 34.1 | 20.91 | 0.85 | (0.76,0.95) | 0.0035 | |
| Region | | | | | | | | | | | | 0.1261 |
| North America | 873 | 275 | 31.5 | 19.97 | 844 | 217 | 25.7 | 15.37 | 0.77 | (0.64,0.92) | 0.0035 | |
| Europe | 1304 | 462 | 35.4 | 21.13 | 1344 | 447 | 33.3 | 19.80 | 0.92 | (0.81,1.05) | 0.2350 | |
| Japan | 308 | 85 | 27.6 | 15.50 | 304 | 85 | 28.0 | 16.02 | 1.08 | (0.80,1.46) | 0.6035 | |
| Other Asia | 820 | 213 | 26.0 | 16.41 | 812 | 211 | 26.0 | 16.42 | 0.99 | (0.82,1.20) | 0.9521 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.8070 |
| Diabetic | 1515 | 594 | 39.2 | 24.51 | 1525 | 550 | 36.1 | 22.22 | 0.90 | (0.80,1.01) | 0.0734 | |
| Non-diabetic | 1790 | 441 | 24.6 | 14.76 | 1779 | 410 | 23.0 | 13.63 | 0.92 | (0.80,1.05) | 0.2217 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5088 |
| <30 | 1961 | 569 | 29.0 | 17.90 | 1955 | 511 | 26.1 | 15.67 | 0.89 | (0.79,1.00) | 0.0465 | |
| >=30 | 1337 | 464 | 34.7 | 20.91 | 1340 | 447 | 33.4 | 20.26 | 0.94 | (0.83,1.07) | 0.3509 | |
| Prior CV disease | | | | | | | | | | | | 0.3397 |
| No | 2401 | 620 | 25.8 | 15.23 | 2443 | 606 | 24.8 | 14.57 | 0.95 | (0.85,1.06) | 0.3333 | |
| Yes | 904 | 415 | 45.9 | 30.97 | 861 | 354 | 41.1 | 26.73 | 0.87 | (0.75,1.00) | 0.0477 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.4439 |
| <130 | 1208 | 353 | 29.2 | 17.60 | 1190 | 331 | 27.8 | 16.81 | 0.95 | (0.82,1.11) | 0.5332 | |
| >=130 | 2097 | 682 | 32.5 | 20.03 | 2114 | 629 | 29.8 | 17.89 | 0.89 | (0.80,0.99) | 0.0300 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2990 |
| <75 | 1286 | 484 | 37.6 | 23.75 | 1294 | 439 | 33.9 | 20.69 | 0.87 | (0.76,0.99) | 0.0309 | |
| 75 to <85 | 1033 | 278 | 26.9 | 15.65 | 1019 | 273 | 26.8 | 15.87 | 1.01 | (0.86,1.20) | 0.8640 | |
| >=85 | 986 | 273 | 27.7 | 17.11 | 991 | 248 | 25.0 | 15.10 | 0.87 | (0.73,1.03) | 0.1130 | |
| History of heart failure | | | | | | | | | | | | 0.9925 |
| No | 2970 | 860 | 29.0 | 17.43 | 2979 | 801 | 26.9 | 15.94 | 0.91 | (0.83,1.00) | 0.0554 | |
| Yes | 334 | 175 | 52.4 | 36.89 | 324 | 158 | 48.8 | 34.45 | 0.91 | (0.73,1.13) | 0.3974 | |
| History of renal disease | | | | | | | | | | | | 0.5687 |
| Diabetic kidney disease | 1025 | 404 | 39.4 | 24.60 | 1032 | 368 | 35.7 | 21.89 | 0.89 | (0.77,1.02) | 0.0943 | |
| Glomerular disease | 816 | 179 | 21.9 | 13.17 | 853 | 161 | 18.9 | 11.03 | 0.83 | (0.67,1.03) | 0.0918 | |
| Hypertensive/renovascular disease | 739 | 225 | 30.4 | 18.99 | 706 | 208 | 29.5 | 17.62 | 0.92 | (0.76,1.11) | 0.4054 | |
| Other/Unknown | 725 | 227 | 31.3 | 18.55 | 713 | 223 | 31.3 | 19.17 | 1.01 | (0.84,1.21) | 0.9253 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2374 |
| <30 | 1151 | 436 | 37.9 | 23.78 | 1131 | 409 | 36.2 | 22.65 | 0.95 | (0.83,1.09) | 0.4920 | |
| 30 to <45 | 1461 | 448 | 30.7 | 18.49 | 1467 | 390 | 26.6 | 15.65 | 0.84 | (0.73,0.96) | 0.0117 | |
| >=45 | 693 | 151 | 21.8 | 13.10 | 706 | 161 | 22.8 | 13.57 | 1.02 | (0.82,1.28) | 0.8371 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.3492 |
| Normal (<30) | 663 | 234 | 35.3 | 21.73 | 665 | 197 | 29.6 | 17.87 | 0.83 | (0.68,1.00) | 0.0486 | |
| Microalbuminuria (30 to <=300) | 937 | 298 | 31.8 | 19.37 | 927 | 265 | 28.6 | 17.23 | 0.88 | (0.74,1.03) | 0.1146 | |
| Macroalbuminuria (>300) | 1705 | 503 | 29.5 | 18.00 | 1712 | 498 | 29.1 | 17.51 | 0.97 | (0.85,1.09) | 0.5874 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7503 |
| Low, moderate or high | 833 | 230 | 27.6 | 16.67 | 839 | 209 | 24.9 | 14.83 | 0.89 | (0.73,1.07) | 0.2062 | |
| Very high | 2472 | 805 | 32.6 | 19.98 | 2465 | 751 | 30.5 | 18.43 | 0.92 | (0.83,1.01) | 0.0888 | |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | 0.2060 |
| No | 508 | 204 | 40.2 | 27.28 | 473 | 160 | 33.8 | 21.76 | 0.81 | (0.66,0.99) | 0.0428 | |
| Yes | 2797 | 831 | 29.7 | 17.82 | 2831 | 800 | 28.3 | 16.85 | 0.94 | (0.85,1.03) | 0.1799 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5163 |
| No | 1940 | 505 | 26.0 | 15.47 | 1908 | 461 | 24.2 | 14.26 | 0.93 | (0.82,1.06) | 0.2735 | |
| Yes | 1365 | 530 | 38.8 | 24.69 | 1396 | 499 | 35.7 | 22.16 | 0.88 | (0.78,0.99) | 0.0390 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.4437 |
| No | 1852 | 451 | 24.4 | 14.54 | 1942 | 459 | 23.6 | 13.97 | 0.95 | (0.84,1.09) | 0.4796 | |
| Yes | 1453 | 584 | 40.2 | 25.31 | 1362 | 501 | 36.8 | 22.79 | 0.89 | (0.79,1.00) | 0.0571 | |

* Based on a Cox regression model with terms age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.3.6: 1**

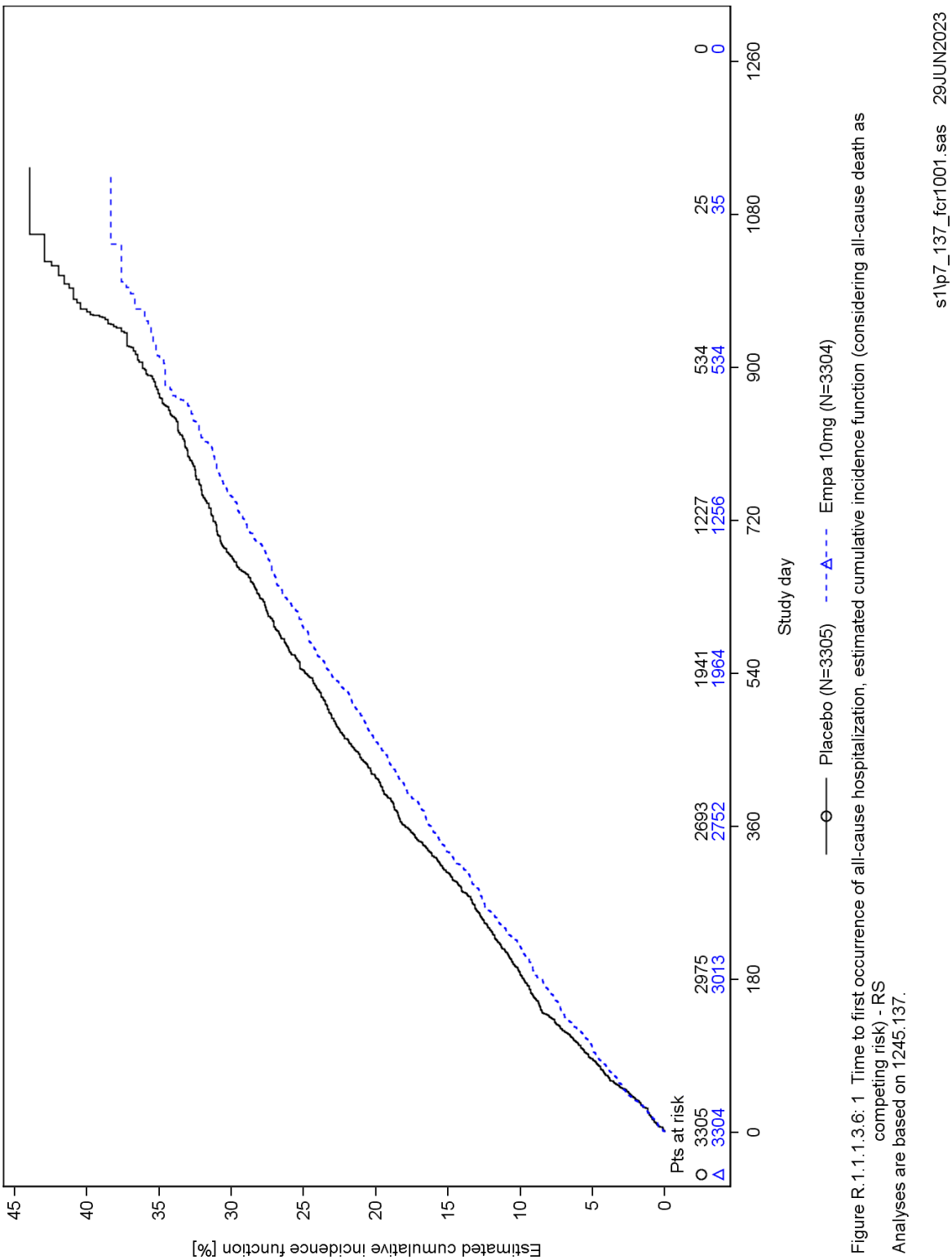


Figure R.1.1.1.3.6: 1 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.3.6: 2**

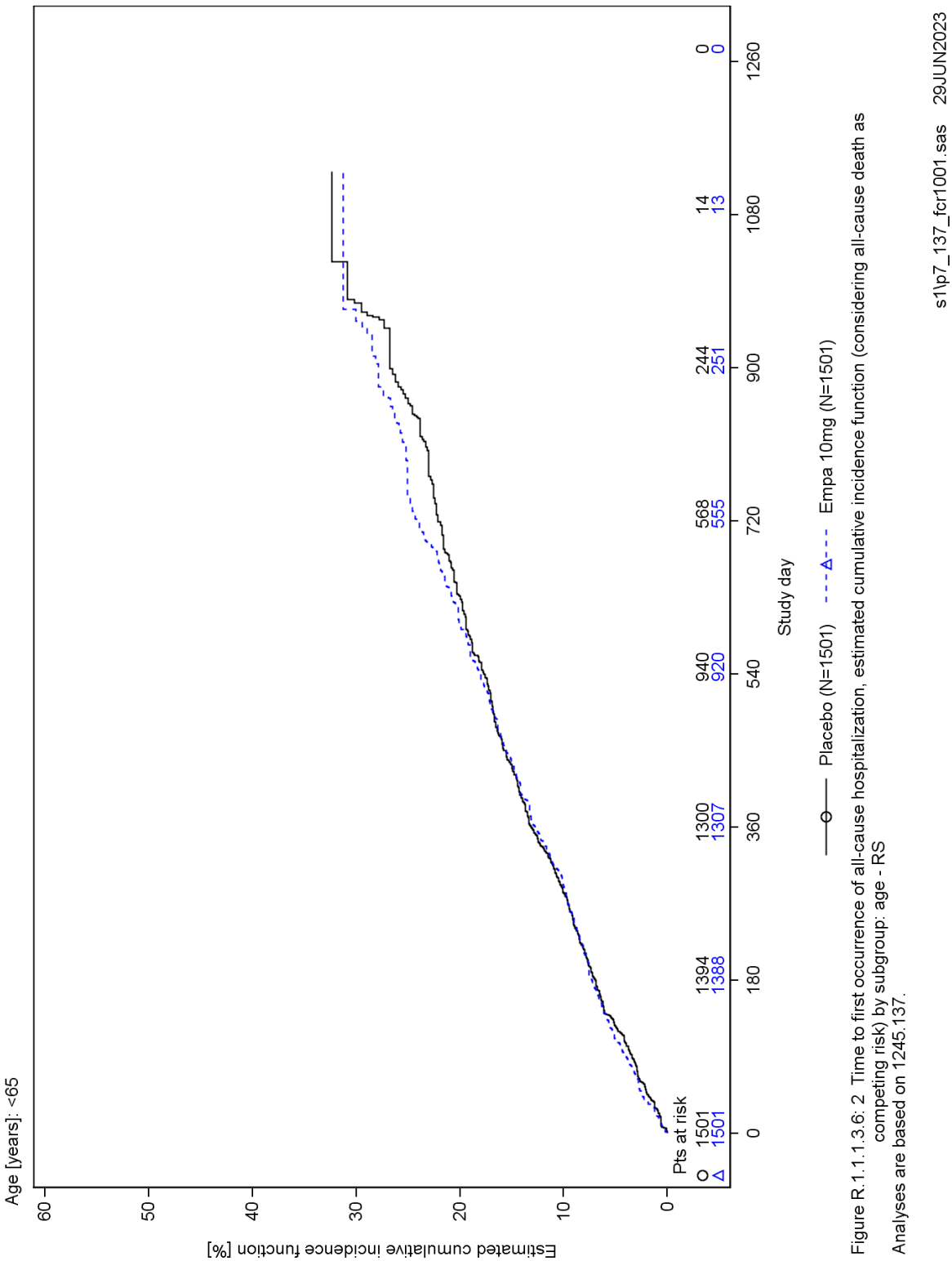


Figure R.1.1.1.3.6: 2 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: age - RS

Analyses are based on 1245.137.

**Figure R.1.1.1.3.6: 2**

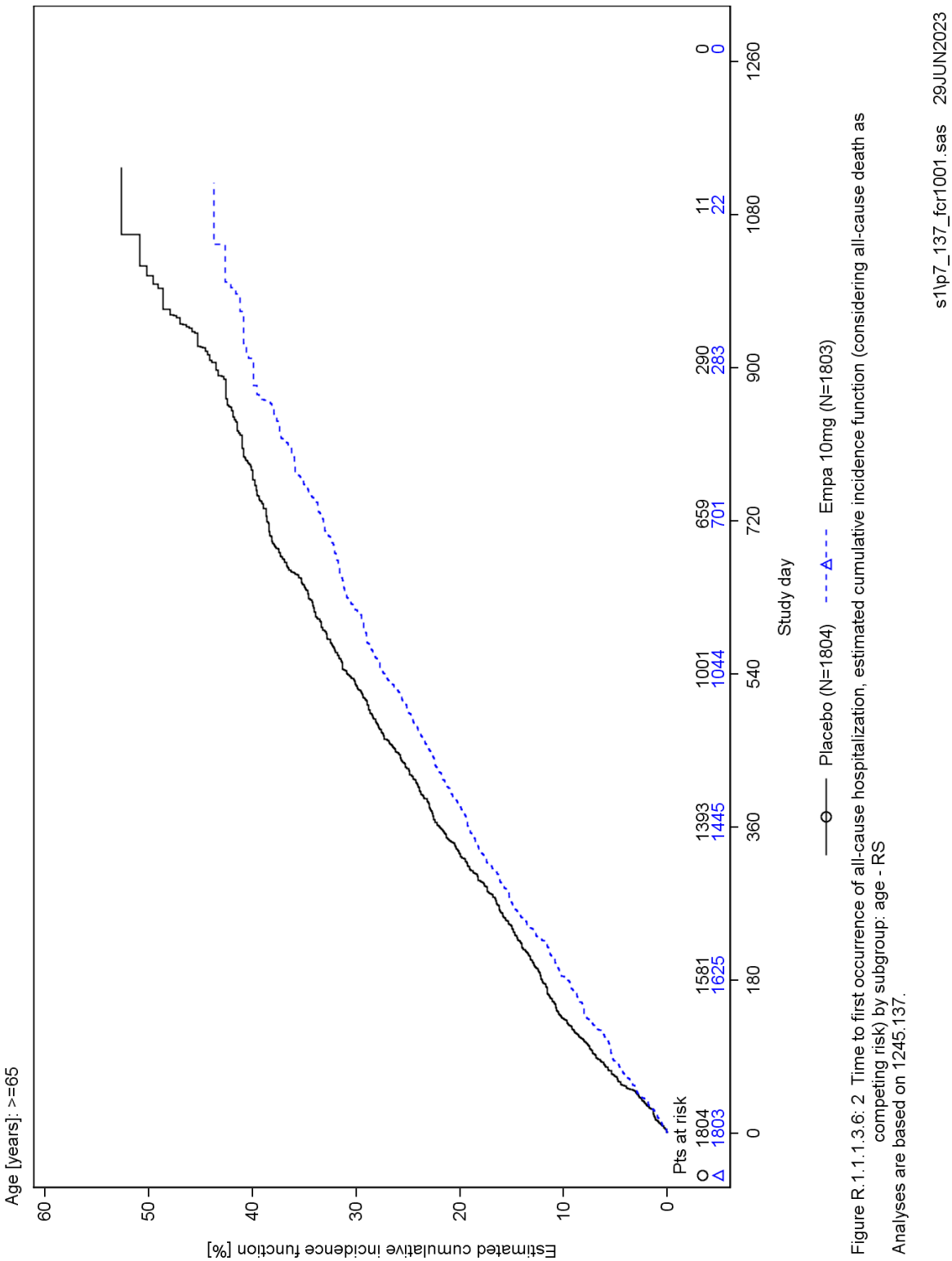


Figure R.1.1.1.3.6: 2 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: age - RS

Analyses are based on 1245.137.

R.1.1.1.3.7 Time to occurrence of all-cause hospitalizations (first and recurrent)

Table R.1.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3305 | 1035 | 31.3 | 1895 | 29.22 | 3304 | 960 | 29.1 | 1611 | 24.80 | 0.86 | (0.78,0.95) | 0.0025 | |
| Sex | | | | | | | | | | | | | | 0.0957 |
| Male | 2210 | 704 | 31.9 | 1315 | 30.31 | 2207 | 676 | 30.6 | 1155 | 26.60 | 0.91 | (0.81,1.02) | 0.1151 | |
| Female | 1095 | 331 | 30.2 | 580 | 27.03 | 1097 | 284 | 25.9 | 456 | 21.17 | 0.76 | (0.63,0.90) | 0.0021 | |
| Age [years] | | | | | | | | | | | | | | 0.0654 |
| <65 | 1501 | 332 | 22.1 | 573 | 19.66 | 1501 | 345 | 23.0 | 558 | 19.13 | 0.97 | (0.83,1.14) | 0.7115 | |
| >=65 | 1804 | 703 | 39.0 | 1322 | 37.02 | 1803 | 615 | 34.1 | 1053 | 29.43 | 0.80 | (0.70,0.91) | 0.0006 | |
| Region | | | | | | | | | | | | | | 0.3148 |
| North America | 873 | 275 | 31.5 | 422 | 25.77 | 844 | 217 | 25.7 | 350 | 21.80 | 0.82 | (0.67,1.01) | 0.0560 | |
| Europe | 1304 | 462 | 35.4 | 954 | 35.26 | 1344 | 447 | 33.3 | 791 | 28.54 | 0.80 | (0.69,0.93) | 0.0037 | |
| Japan | 308 | 85 | 27.6 | 158 | 24.46 | 304 | 85 | 28.0 | 131 | 20.85 | 1.08 | (0.77,1.50) | 0.6546 | |
| Other Asia | 820 | 213 | 26.0 | 361 | 24.14 | 812 | 211 | 26.0 | 339 | 22.75 | 0.94 | (0.76,1.16) | 0.5842 | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9500 |
| Diabetic | 1515 | 594 | 39.2 | 1114 | 36.69 | 1525 | 550 | 36.1 | 956 | 31.15 | 0.86 | (0.75,0.98) | 0.0239 | |
| Non-diabetic | 1790 | 441 | 24.6 | 781 | 22.65 | 1779 | 410 | 23.0 | 655 | 19.11 | 0.85 | (0.74,0.98) | 0.0276 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0457 |
| <30 | 1961 | 569 | 29.0 | 1096 | 29.09 | 1955 | 511 | 26.1 | 823 | 21.75 | 0.79 | (0.69,0.89) | 0.0002 | |
| >=30 | 1337 | 464 | 34.7 | 793 | 29.34 | 1340 | 447 | 33.4 | 786 | 29.17 | 0.96 | (0.83,1.11) | 0.5751 | |
| Prior CV disease | | | | | | | | | | | | | | 0.1239 |
| No | 2401 | 620 | 25.8 | 1025 | 21.76 | 2443 | 606 | 24.8 | 968 | 20.19 | 0.92 | (0.82,1.04) | 0.1680 | |
| Yes | 904 | 415 | 45.9 | 870 | 49.06 | 861 | 354 | 41.1 | 643 | 37.78 | 0.79 | (0.67,0.92) | 0.0037 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4027 |
| <130 | 1208 | 353 | 29.2 | 637 | 26.91 | 1190 | 331 | 27.8 | 561 | 24.12 | 0.91 | (0.77,1.07) | 0.2375 | |
| >=130 | 2097 | 682 | 32.5 | 1258 | 30.55 | 2114 | 629 | 29.8 | 1050 | 25.18 | 0.83 | (0.74,0.94) | 0.0025 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, local screening eGFR (CKD-EPI), log(local screening UACR), subgroup, screening diabetes status (2 cat.), sex, region, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1872 |
| <75 | 1286 | 484 | 37.6 | 928 | 36.62 | 1294 | 439 | 33.9 | 742 | 28.72 | 0.80 | (0.69,0.93) | 0.0036 | |
| 75 to <85 | 1033 | 278 | 26.9 | 477 | 23.27 | 1019 | 273 | 26.8 | 471 | 23.37 | 0.99 | (0.83,1.19) | 0.9254 | |
| >=85 | 986 | 273 | 27.7 | 490 | 25.78 | 991 | 248 | 25.0 | 398 | 20.99 | 0.83 | (0.69,1.00) | 0.0530 | |
| History of heart failure | | | | | | | | | | | | | | 0.6875 |
| No | 2970 | 860 | 29.0 | 1519 | 26.09 | 2979 | 801 | 26.9 | 1319 | 22.52 | 0.87 | (0.78,0.96) | 0.0072 | |
| Yes | 334 | 175 | 52.4 | 376 | 56.82 | 324 | 158 | 48.8 | 291 | 45.82 | 0.82 | (0.63,1.06) | 0.1328 | |
| History of renal disease | | | | | | | | | | | | | | 0.2278 |
| Diabetic kidney disease | 1025 | 404 | 39.4 | 724 | 35.30 | 1032 | 368 | 35.7 | 622 | 30.04 | 0.84 | (0.71,0.99) | 0.0374 | |
| Glomerular disease | 816 | 179 | 21.9 | 318 | 20.59 | 853 | 161 | 18.9 | 239 | 14.78 | 0.72 | (0.58,0.90) | 0.0042 | |
| Hypertensive/renovascular disease | 739 | 225 | 30.4 | 422 | 29.59 | 706 | 208 | 29.5 | 381 | 27.04 | 0.89 | (0.72,1.09) | 0.2634 | |
| Other/Unknown | 725 | 227 | 31.3 | 431 | 29.46 | 713 | 223 | 31.3 | 369 | 26.39 | 0.99 | (0.80,1.22) | 0.9321 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6081 |
| <30 | 1151 | 436 | 37.9 | 821 | 36.32 | 1131 | 409 | 36.2 | 716 | 31.99 | 0.88 | (0.76,1.03) | 0.1066 | |
| 30 to <45 | 1461 | 448 | 30.7 | 793 | 27.32 | 1467 | 390 | 26.6 | 646 | 22.30 | 0.81 | (0.70,0.94) | 0.0044 | |
| >=45 | 693 | 151 | 21.8 | 281 | 21.27 | 706 | 161 | 22.8 | 249 | 18.29 | 0.91 | (0.72,1.14) | 0.4079 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6555 |
| Normal (<30) | 663 | 234 | 35.3 | 410 | 30.78 | 665 | 197 | 29.6 | 326 | 24.74 | 0.80 | (0.65,0.99) | 0.0439 | |
| Microalbuminuria (30 to <=300) | 937 | 298 | 31.8 | 563 | 30.50 | 927 | 265 | 28.6 | 451 | 24.61 | 0.83 | (0.69,0.99) | 0.0434 | |
| Macroalbuminuria (>300) | 1705 | 503 | 29.5 | 922 | 27.88 | 1712 | 498 | 29.1 | 834 | 24.93 | 0.89 | (0.78,1.02) | 0.1063 | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.6411 |
| Low, moderate or high | 833 | 230 | 27.6 | 401 | 24.46 | 839 | 209 | 24.9 | 341 | 20.92 | 0.89 | (0.73,1.09) | 0.2619 | |
| Very high | 2472 | 805 | 32.6 | 1494 | 30.83 | 2465 | 751 | 30.5 | 1270 | 26.10 | 0.84 | (0.75,0.94) | 0.0025 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, local screening eGFR (CKD-EPI), log(local screening UACR), subgroup, screening diabetes status (2 cat.), sex, region, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

Table R.1.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline use of RAS inhibitor** | | | | | | | | | | | | | | 0.2633 |
| No | 508 | 204 | 40.2 | 380 | 39.95 | 473 | 160 | 33.8 | 288 | 32.30 | 0.76 | (0.60,0.96) | 0.0239 | |
| Yes | 2797 | 831 | 29.7 | 1515 | 27.38 | 2831 | 800 | 28.3 | 1323 | 23.61 | 0.88 | (0.80,0.98) | 0.0213 | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3269 |
| No | 1940 | 505 | 26.0 | 890 | 23.59 | 1908 | 461 | 24.2 | 751 | 20.24 | 0.90 | (0.78,1.03) | 0.1175 | |
| Yes | 1365 | 530 | 38.8 | 1005 | 37.06 | 1396 | 499 | 35.7 | 860 | 30.89 | 0.81 | (0.70,0.94) | 0.0043 | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1928 |
| No | 1852 | 451 | 24.4 | 757 | 21.23 | 1942 | 459 | 23.6 | 719 | 19.22 | 0.93 | (0.81,1.06) | 0.2839 | |
| Yes | 1453 | 584 | 40.2 | 1138 | 38.99 | 1362 | 501 | 36.8 | 892 | 32.38 | 0.81 | (0.71,0.93) | 0.0033 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, local screening eGFR (CKD-EPI), log(local screening UACR), subgroup, screening diabetes status (2 cat.), sex, region, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.137.
** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.

**Figure R.1.1.1.3.7: 1**

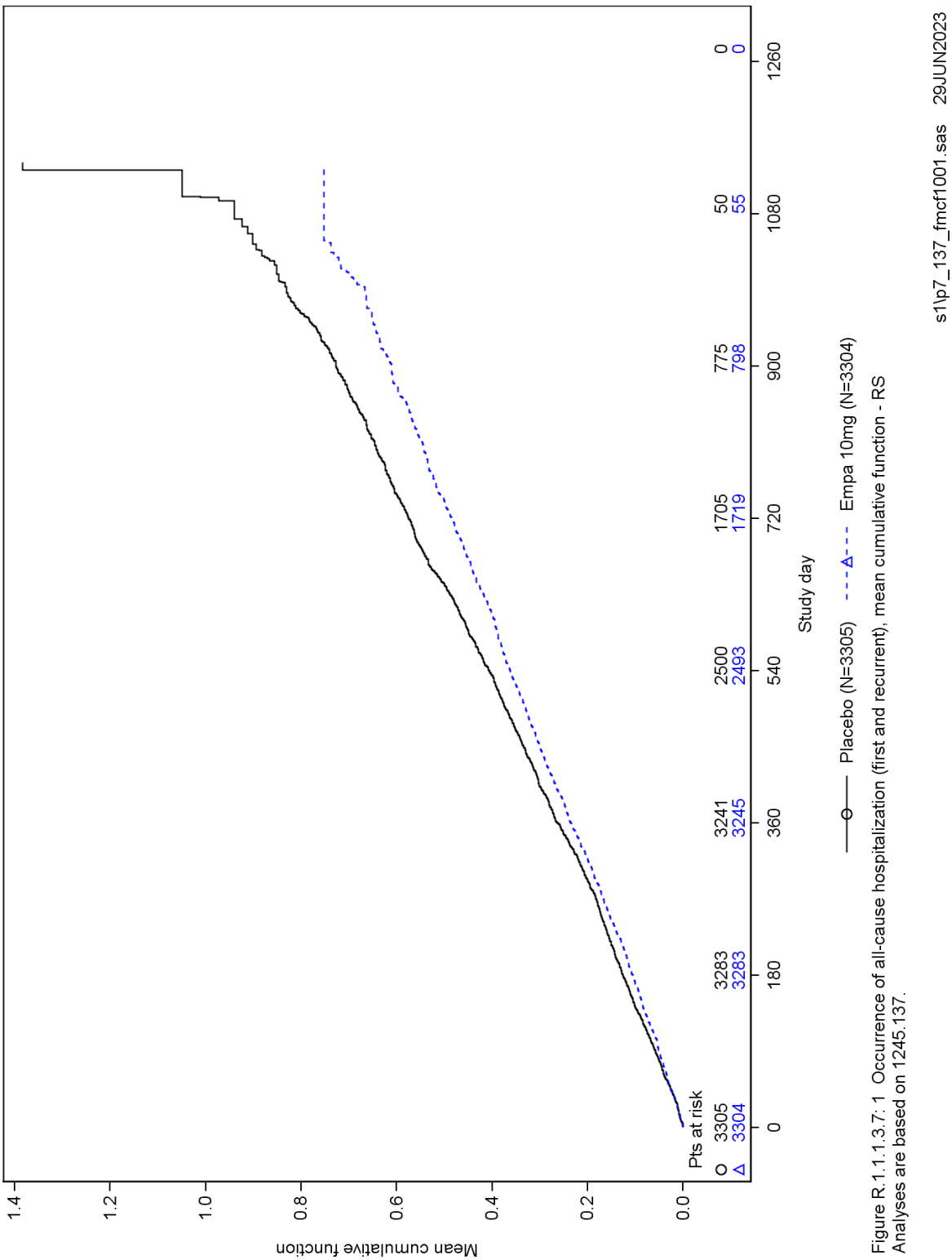


Figure R.1.1.1.3.7: 1 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.3.7: 2**

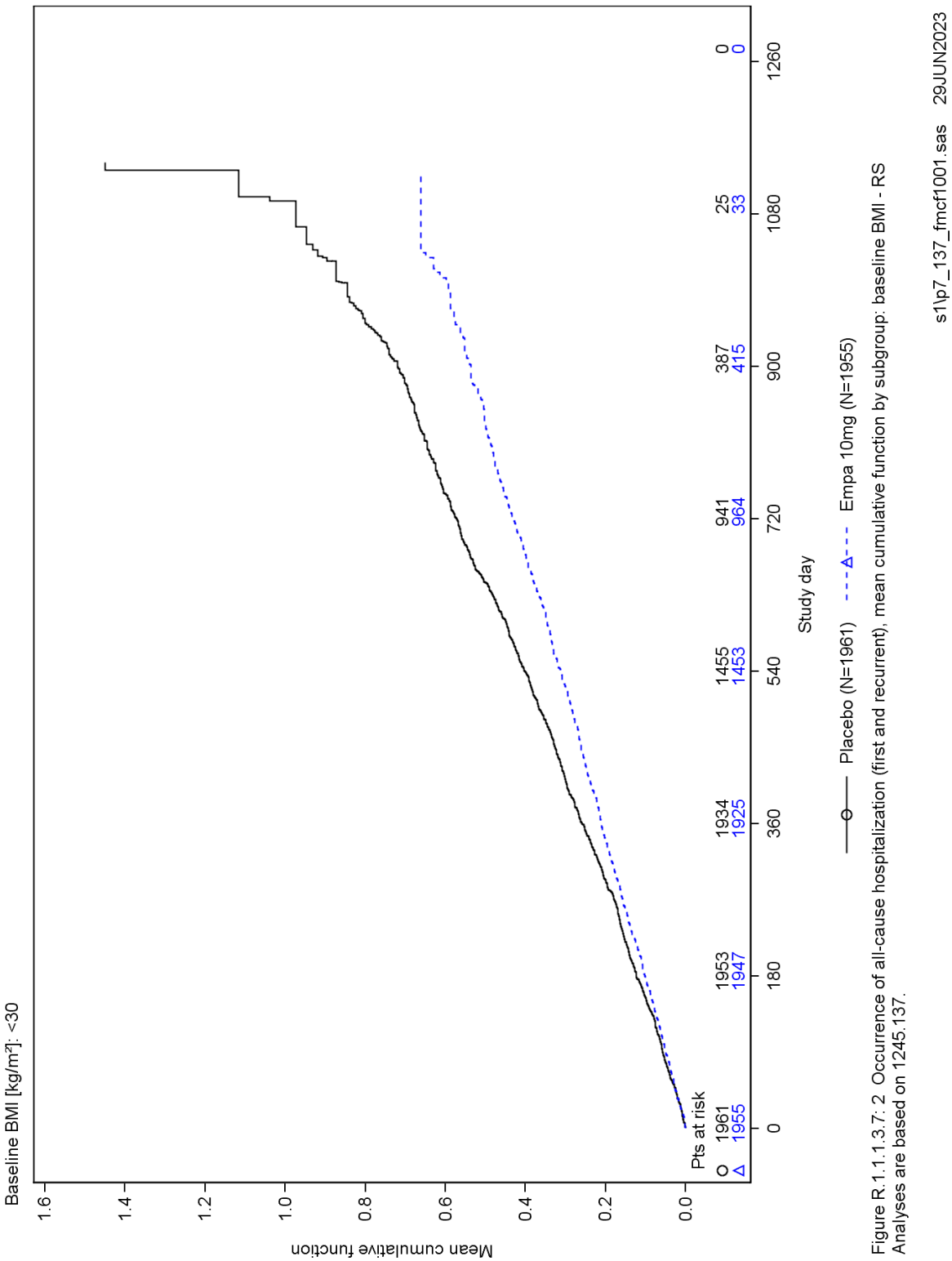


Figure R.1.1.1.3.7: 2 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: baseline BMI - RS
Analyses are based on 1245.137.

**Figure R.1.1.1.3.7: 2**

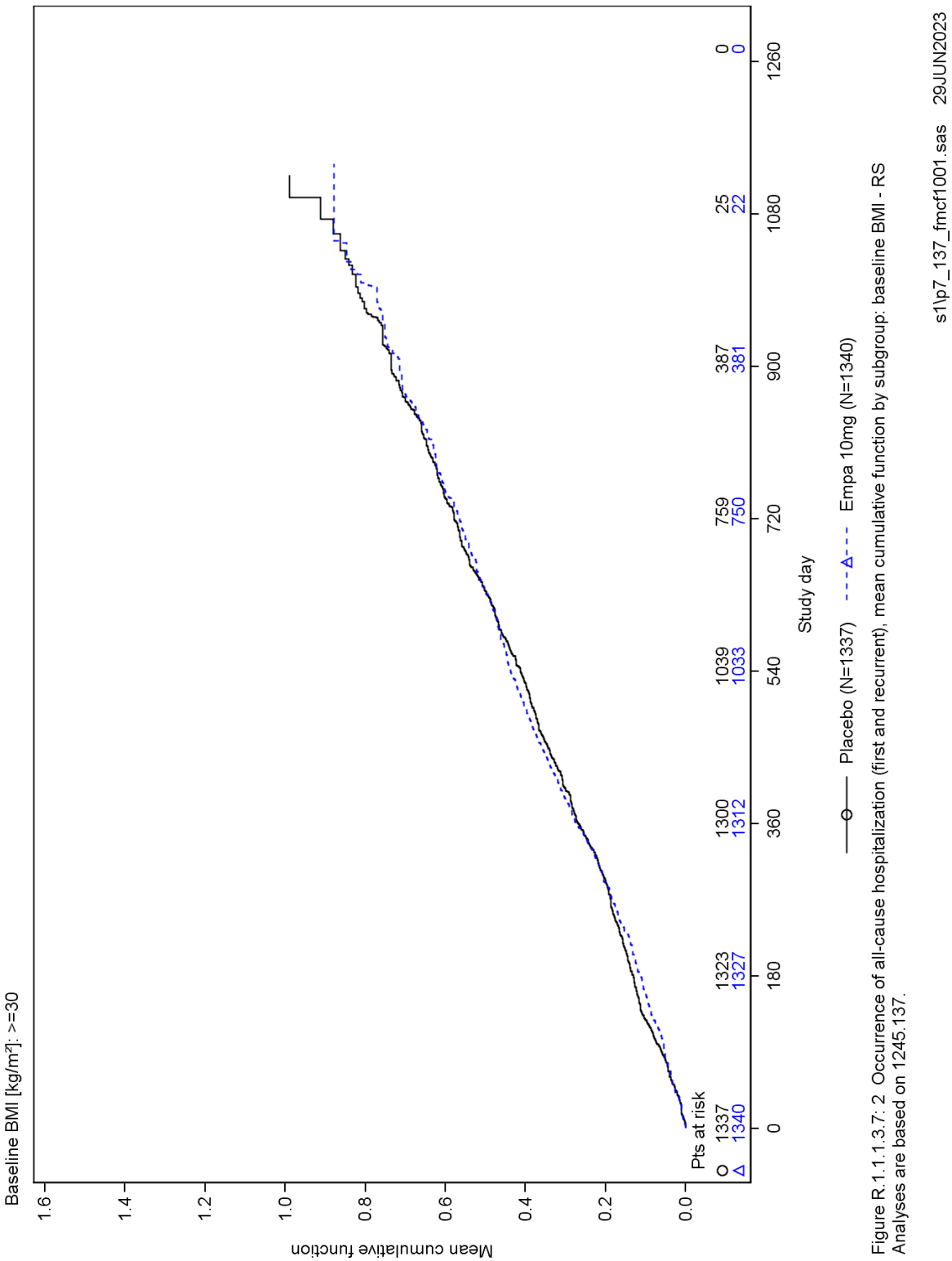


Figure R.1.1.1.3.7: 2 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: baseline BMI - RS
Analyses are based on 1245.137.

**R.1.1.2**

R.1.1.2.1 Responder analyses based on last value during follow-up period

R.1.1.2.1.1 EQ-VAS responder analysis (15 points)

Table R.1.1.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during follow-up period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3129 | 618 | 19.8 | 3146 | 599 | 19.0 | 0.99 | (0.90,1.10) | 0.9142 | 0.99 | (0.87,1.13) | |
| Sex | | | | | | | | | | | | 0.3707 |
| Male | 2093 | 387 | 18.5 | 2100 | 395 | 18.8 | 1.03 | (0.91,1.16) | 0.6578 | 1.04 | (0.88,1.22) | |
| Female | 1036 | 231 | 22.3 | 1046 | 204 | 19.5 | 0.94 | (0.80,1.10) | 0.4303 | 0.91 | (0.73,1.14) | |
| Age [years] | | | | | | | | | | | | 0.6223 |
| <65 | 1458 | 241 | 16.5 | 1461 | 244 | 16.7 | 1.02 | (0.87,1.20) | 0.7754 | 1.03 | (0.84,1.26) | |
| >=65 | 1671 | 377 | 22.6 | 1685 | 355 | 21.1 | 0.97 | (0.86,1.10) | 0.6635 | 0.96 | (0.81,1.14) | |
| Region | | | | | | | | | | | | 0.2100 |
| North America | 796 | 149 | 18.7 | 781 | 146 | 18.7 | 1.02 | (0.84,1.25) | 0.8139 | 1.03 | (0.80,1.34) | |
| Europe | 1231 | 286 | 23.2 | 1279 | 296 | 23.1 | 1.04 | (0.90,1.19) | 0.6081 | 1.04 | (0.86,1.27) | |
| Japan | 296 | 58 | 19.6 | 291 | 33 | 11.3 | 0.67 | (0.46,0.98) | 0.0402 | 0.61 | (0.38,0.98) | |
| Other Asia | 806 | 125 | 15.5 | 795 | 124 | 15.6 | 1.00 | (0.81,1.24) | 0.9945 | 1.00 | (0.76,1.32) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1875 |
| Diabetic | 1398 | 321 | 23.0 | 1427 | 294 | 20.6 | 0.93 | (0.81,1.07) | 0.2987 | 0.90 | (0.75,1.08) | |
| Non-diabetic | 1731 | 297 | 17.2 | 1719 | 305 | 17.7 | 1.06 | (0.92,1.22) | 0.4060 | 1.08 | (0.90,1.30) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1099 |
| <30 | 1884 | 359 | 19.1 | 1875 | 314 | 16.7 | 0.92 | (0.80,1.05) | 0.2055 | 0.89 | (0.75,1.06) | |
| >=30 | 1239 | 259 | 20.9 | 1263 | 280 | 22.2 | 1.08 | (0.93,1.25) | 0.3123 | 1.10 | (0.90,1.35) | |
| Prior CV disease | | | | | | | | | | | | 0.1600 |
| No | 2304 | 418 | 18.1 | 2349 | 435 | 18.5 | 1.05 | (0.93,1.17) | 0.4572 | 1.06 | (0.91,1.24) | |
| Yes | 825 | 200 | 24.2 | 797 | 164 | 20.6 | 0.90 | (0.75,1.07) | 0.2326 | 0.85 | (0.66,1.09) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.2834 |
| <130 | 1144 | 208 | 18.2 | 1129 | 213 | 18.9 | 1.07 | (0.91,1.27) | 0.4216 | 1.09 | (0.88,1.36) | |
| >=130 | 1985 | 410 | 20.7 | 2017 | 386 | 19.1 | 0.96 | (0.85,1.08) | 0.4708 | 0.94 | (0.80,1.10) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms Baseline EQ-VAS score, treatment, region, age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.137.
****Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.

Table R.1.1.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during follow-up period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6454 |
| <75 | 1206 | 254 | 21.1 | 1204 | 238 | 19.8 | 0.98 | (0.84,1.14) | 0.7462 | 0.96 | (0.78,1.18) | |
| 75 to <85 | 970 | 185 | 19.1 | 980 | 194 | 19.8 | 1.06 | (0.89,1.27) | 0.4838 | 1.08 | (0.86,1.37) | |
| >=85 | 953 | 179 | 18.8 | 962 | 167 | 17.4 | 0.95 | (0.79,1.14) | 0.5890 | 0.94 | (0.73,1.19) | |
| History of heart failure | | | | | | | | | | | | 0.7715 |
| No | 2824 | 549 | 19.4 | 2856 | 539 | 18.9 | 1.00 | (0.90,1.11) | 0.9890 | 1.00 | (0.87,1.15) | |
| Yes | 304 | 69 | 22.7 | 290 | 60 | 20.7 | 0.96 | (0.71,1.29) | 0.7623 | 0.93 | (0.62,1.41) | |
| History of renal disease | | | | | | | | | | | | 0.3674 |
| Diabetic kidney disease | 942 | 209 | 22.2 | 963 | 203 | 21.1 | 0.97 | (0.83,1.15) | 0.7615 | 0.96 | (0.76,1.21) | |
| Glomerular disease | 799 | 123 | 15.4 | 840 | 127 | 15.1 | 1.01 | (0.81,1.27) | 0.9014 | 1.02 | (0.77,1.34) | |
| Hypertensive/renovascular disease | 697 | 126 | 18.1 | 673 | 136 | 20.2 | 1.15 | (0.93,1.41) | 0.1938 | 1.20 | (0.90,1.58) | |
| Other/Unknown | 691 | 160 | 23.2 | 670 | 133 | 19.9 | 0.89 | (0.73,1.08) | 0.2418 | 0.85 | (0.65,1.12) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6899 |
| <30 | 1063 | 247 | 23.2 | 1059 | 235 | 22.2 | 0.98 | (0.84,1.14) | 0.7591 | 0.97 | (0.78,1.19) | |
| 30 to <45 | 1387 | 276 | 19.9 | 1395 | 258 | 18.5 | 0.98 | (0.85,1.14) | 0.7903 | 0.97 | (0.80,1.18) | |
| >=45 | 679 | 95 | 14.0 | 692 | 106 | 15.3 | 1.10 | (0.86,1.41) | 0.4447 | 1.13 | (0.83,1.53) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7510 |
| Normal (<30) | 629 | 134 | 21.3 | 626 | 136 | 21.7 | 1.07 | (0.87,1.31) | 0.5446 | 1.09 | (0.83,1.45) | |
| Microalbuminuria (30 to <=300) | 882 | 177 | 20.1 | 880 | 167 | 19.0 | 0.97 | (0.81,1.17) | 0.7605 | 0.96 | (0.75,1.23) | |
| Macroalbuminuria (>300) | 1618 | 307 | 19.0 | 1640 | 296 | 18.0 | 0.97 | (0.85,1.12) | 0.7194 | 0.96 | (0.80,1.16) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5301 |
| Low, moderate or high | 806 | 134 | 16.6 | 812 | 140 | 17.2 | 1.06 | (0.86,1.30) | 0.6117 | 1.07 | (0.82,1.41) | |
| Very high | 2323 | 484 | 20.8 | 2334 | 459 | 19.7 | 0.98 | (0.88,1.09) | 0.7006 | 0.97 | (0.83,1.12) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms Baseline EQ-VAS score, treatment, region, age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.137.
****Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.

Table R.1.1.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during follow-up period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of RAS inhibitor**** | | | | | | | | | | | | 0.3101 |
| No | 466 | 107 | 23.0 | 439 | 90 | 20.5 | 0.89 | (0.70,1.13) | 0.3297 | 0.85 | (0.61,1.19) | |
| Yes | 2663 | 511 | 19.2 | 2707 | 509 | 18.8 | 1.02 | (0.91,1.13) | 0.7581 | 1.02 | (0.88,1.17) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6015 |
| No | 1862 | 349 | 18.7 | 1825 | 341 | 18.7 | 1.02 | (0.89,1.16) | 0.7941 | 1.02 | (0.86,1.21) | |
| Yes | 1267 | 269 | 21.2 | 1321 | 258 | 19.5 | 0.97 | (0.83,1.12) | 0.6422 | 0.95 | (0.78,1.16) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3354 |
| No | 1788 | 324 | 18.1 | 1868 | 312 | 16.7 | 0.95 | (0.83,1.09) | 0.4989 | 0.94 | (0.79,1.12) | |
| Yes | 1341 | 294 | 21.9 | 1278 | 287 | 22.5 | 1.05 | (0.91,1.21) | 0.4928 | 1.07 | (0.88,1.29) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms Baseline EQ-VAS score, treatment, region, age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.137.
****Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.

Table R.1.1.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during follow-up period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3129 | 460 | 14.7 | 3146 | 500 | 15.9 | 1.00 | (0.90,1.12) | 0.9579 | 0.99 | (0.84,1.16) | |
| Sex | | | | | | | | | | | | 0.5100 |
| Male | 2093 | 308 | 14.7 | 2100 | 321 | 15.3 | 1.03 | (0.90,1.19) | 0.6766 | 1.00 | (0.82,1.22) | |
| Female | 1036 | 152 | 14.7 | 1046 | 179 | 17.1 | 0.95 | (0.79,1.15) | 0.6083 | 0.96 | (0.73,1.27) | |
| Age [years] | | | | | | | | | | | | 0.0985 |
| <65 | 1458 | 231 | 15.8 | 1461 | 221 | 15.1 | 0.91 | (0.78,1.06) | 0.2087 | 0.88 | (0.70,1.11) | |
| >=65 | 1671 | 229 | 13.7 | 1685 | 279 | 16.6 | 1.09 | (0.93,1.28) | 0.2787 | 1.10 | (0.88,1.38) | |
| Region | | | | | | | | | | | | 0.1696 |
| North America | 796 | 134 | 16.8 | 781 | 132 | 16.9 | 0.95 | (0.77,1.18) | 0.6598 | 0.91 | (0.66,1.25) | |
| Europe | 1231 | 167 | 13.6 | 1279 | 197 | 15.4 | 1.06 | (0.88,1.28) | 0.5323 | 1.03 | (0.79,1.35) | |
| Japan | 296 | 37 | 12.5 | 291 | 66 | 22.7 | 1.35 | (0.93,1.95) | 0.1160 | 1.72 | (1.05,2.81) | |
| Other Asia | 806 | 122 | 15.1 | 795 | 105 | 13.2 | 0.86 | (0.69,1.06) | 0.1578 | 0.81 | (0.59,1.10) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1404 |
| Diabetic | 1398 | 242 | 17.3 | 1427 | 247 | 17.3 | 0.92 | (0.79,1.08) | 0.3300 | 0.85 | (0.68,1.08) | |
| Non-diabetic | 1731 | 218 | 12.6 | 1719 | 253 | 14.7 | 1.09 | (0.93,1.28) | 0.2674 | 1.13 | (0.91,1.42) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0232 |
| <30 | 1884 | 244 | 13.0 | 1875 | 295 | 15.7 | 1.13 | (0.97,1.32) | 0.1116 | 1.14 | (0.93,1.41) | |
| >=30 | 1239 | 212 | 17.1 | 1263 | 204 | 16.2 | 0.87 | (0.74,1.03) | 0.1056 | 0.82 | (0.63,1.05) | |
| Prior CV disease | | | | | | | | | | | | 0.2818 |
| No | 2304 | 308 | 13.4 | 2349 | 341 | 14.5 | 0.96 | (0.84,1.10) | 0.5422 | 0.97 | (0.80,1.17) | |
| Yes | 825 | 152 | 18.4 | 797 | 159 | 19.9 | 1.10 | (0.89,1.35) | 0.3725 | 1.04 | (0.77,1.40) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.6083 |
| <130 | 1144 | 182 | 15.9 | 1129 | 185 | 16.4 | 0.97 | (0.81,1.15) | 0.7096 | 0.93 | (0.72,1.21) | |
| >=130 | 1985 | 278 | 14.0 | 2017 | 315 | 15.6 | 1.03 | (0.89,1.19) | 0.7234 | 1.02 | (0.84,1.25) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms Baseline EQ-VAS score, treatment, region, age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.137.
****Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.

Table R.1.1.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during follow-up period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6462 |
| <75 | 1206 | 184 | 15.3 | 1204 | 215 | 17.9 | 1.05 | (0.88,1.25) | 0.5665 | 1.11 | (0.86,1.43) | |
| 75 to <85 | 970 | 135 | 13.9 | 980 | 143 | 14.6 | 1.01 | (0.82,1.25) | 0.9158 | 1.00 | (0.74,1.35) | |
| >=85 | 953 | 141 | 14.8 | 962 | 142 | 14.8 | 0.93 | (0.75,1.14) | 0.4667 | 0.85 | (0.63,1.13) | |
| History of heart failure | | | | | | | | | | | | 0.6125 |
| No | 2824 | 391 | 13.8 | 2856 | 436 | 15.3 | 1.02 | (0.90,1.15) | 0.7969 | 1.03 | (0.86,1.22) | |
| Yes | 304 | 69 | 22.7 | 290 | 64 | 22.1 | 0.94 | (0.70,1.25) | 0.6587 | 0.75 | (0.47,1.20) | |
| History of renal disease | | | | | | | | | | | | 0.3832 |
| Diabetic kidney disease | 942 | 165 | 17.5 | 963 | 169 | 17.5 | 0.91 | (0.75,1.10) | 0.3283 | 0.86 | (0.65,1.14) | |
| Glomerular disease | 799 | 106 | 13.3 | 840 | 118 | 14.0 | 0.98 | (0.79,1.22) | 0.8430 | 0.92 | (0.67,1.26) | |
| Hypertensive/renovascular disease | 697 | 109 | 15.6 | 673 | 107 | 15.9 | 1.04 | (0.82,1.34) | 0.7312 | 0.98 | (0.70,1.38) | |
| Other/Unknown | 691 | 80 | 11.6 | 670 | 106 | 15.8 | 1.19 | (0.93,1.53) | 0.1634 | 1.39 | (0.97,2.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1781 |
| <30 | 1063 | 140 | 13.2 | 1059 | 179 | 16.9 | 1.16 | (0.96,1.40) | 0.1199 | 1.27 | (0.95,1.68) | |
| 30 to <45 | 1387 | 217 | 15.6 | 1395 | 220 | 15.8 | 0.93 | (0.78,1.11) | 0.4203 | 0.86 | (0.67,1.09) | |
| >=45 | 679 | 103 | 15.2 | 692 | 101 | 14.6 | 0.93 | (0.73,1.18) | 0.5303 | 0.91 | (0.65,1.29) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.6144 |
| Normal (<30) | 629 | 92 | 14.6 | 626 | 97 | 15.5 | 0.98 | (0.76,1.25) | 0.8609 | 0.98 | (0.68,1.41) | |
| Microalbuminuria (30 to <=300) | 882 | 137 | 15.5 | 880 | 140 | 15.9 | 0.92 | (0.75,1.15) | 0.4778 | 0.88 | (0.65,1.19) | |
| Macroalbuminuria (>300) | 1618 | 231 | 14.3 | 1640 | 263 | 16.0 | 1.05 | (0.90,1.23) | 0.5068 | 1.06 | (0.85,1.32) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5838 |
| Low, moderate or high | 806 | 124 | 15.4 | 812 | 124 | 15.3 | 0.95 | (0.76,1.18) | 0.6302 | 0.94 | (0.69,1.29) | |
| Very high | 2323 | 336 | 14.5 | 2334 | 376 | 16.1 | 1.02 | (0.89,1.16) | 0.7917 | 1.01 | (0.84,1.22) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms Baseline EQ-VAS score, treatment, region, age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.137.
****Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.

Table R.1.1.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during follow-up period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of RAS inhibitor**** | | | | | | | | | | | | 0.0464 |
| No | 466 | 76 | 16.3 | 439 | 55 | 12.5 | 0.74 | (0.54,1.02) | 0.0662 | 0.58 | (0.37,0.91) | |
| Yes | 2663 | 384 | 14.4 | 2707 | 445 | 16.4 | 1.05 | (0.93,1.18) | 0.4391 | 1.07 | (0.90,1.27) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4700 |
| No | 1862 | 251 | 13.5 | 1825 | 260 | 14.2 | 0.96 | (0.83,1.12) | 0.6445 | 0.97 | (0.78,1.21) | |
| Yes | 1267 | 209 | 16.5 | 1321 | 240 | 18.2 | 1.05 | (0.89,1.24) | 0.5771 | 1.01 | (0.79,1.29) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.8635 |
| No | 1788 | 257 | 14.4 | 1868 | 293 | 15.7 | 0.99 | (0.85,1.15) | 0.8826 | 0.99 | (0.80,1.22) | |
| Yes | 1341 | 203 | 15.1 | 1278 | 207 | 16.2 | 1.01 | (0.85,1.20) | 0.9204 | 0.96 | (0.74,1.24) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms Baseline EQ-VAS score, treatment, region, age (5 cat.), sex, screening diabetes status (2 cat.), local screening eGFR (CKD-EPI) (5 cat.), local screening UACR (5 cat.), subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.137.
****Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.

**R.1.2**

**R.1.2.1**

R.1.2.1 Adverse events overall

Table R.1.2.1: 1 Proportion of patients with any adverse event occurring up to the final follow-up visit, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 1580 | 47.8 | 3304 | 1513 | 45.8 | 0.1010 | 0.96 | (0.91, 1.01) | 0.92 | (0.84,1.02) | -0.02 | (-0.04, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0947 |
| Male | 2210 | 1065 | 48.2 | 2207 | 1050 | 47.6 | 0.6829 | 0.99 | (0.93, 1.05) | 0.98 | (0.87,1.10) | -0.01 | (-0.04, 0.02) | |
| Female | 1095 | 515 | 47.0 | 1097 | 463 | 42.2 | 0.0230 | 0.90 | (0.82, 0.99) | 0.82 | (0.69,0.97) | -0.05 | (-0.09,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6103 |
| <65 | 1501 | 595 | 39.6 | 1501 | 580 | 38.6 | 0.5748 | 0.97 | (0.89, 1.07) | 0.96 | (0.83,1.11) | -0.01 | (-0.04, 0.02) | |
| >=65 | 1804 | 985 | 54.6 | 1803 | 933 | 51.7 | 0.0859 | 0.95 | (0.89, 1.01) | 0.89 | (0.78,1.02) | -0.03 | (-0.06, 0.00) | |
| Region | | | | | | | | | | | | | | 0.1607 |
| North America | 873 | 451 | 51.7 | 844 | 383 | 45.4 | 0.0092 | 0.88 | (0.80, 0.97) | 0.78 | (0.64,0.94) | -0.06 | (-0.11,-0.02) | |
| Europe | 1304 | 712 | 54.6 | 1344 | 735 | 54.7 | 0.9644 | 1.00 | (0.93, 1.07) | 1.00 | (0.86,1.17) | 0.00 | (-0.04, 0.04) | |
| Japan | 308 | 118 | 38.3 | 304 | 119 | 39.1 | 0.8325 | 1.02 | (0.84, 1.25) | 1.04 | (0.75,1.43) | 0.01 | (-0.07, 0.09) | |
| Other Asia | 820 | 299 | 36.5 | 812 | 276 | 34.0 | 0.2957 | 0.93 | (0.82, 1.06) | 0.90 | (0.73,1.10) | -0.02 | (-0.07, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8223 |
| Diabetic | 1515 | 857 | 56.6 | 1525 | 821 | 53.8 | 0.1300 | 0.95 | (0.89, 1.01) | 0.90 | (0.78,1.03) | -0.03 | (-0.06, 0.01) | |
| Non-diabetic | 1790 | 723 | 40.4 | 1779 | 692 | 38.9 | 0.3620 | 0.96 | (0.89, 1.04) | 0.94 | (0.82,1.07) | -0.01 | (-0.05, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5390 |
| <30 | 1961 | 845 | 43.1 | 1955 | 793 | 40.6 | 0.1089 | 0.94 | (0.87, 1.01) | 0.90 | (0.79,1.02) | -0.03 | (-0.06, 0.01) | |
| >=30 | 1337 | 732 | 54.7 | 1340 | 713 | 53.2 | 0.4240 | 0.97 | (0.91, 1.04) | 0.94 | (0.81,1.09) | -0.02 | (-0.05, 0.02) | |
| Prior CV disease | | | | | | | | | | | | | | 0.5604 |
| No | 2401 | 1012 | 42.1 | 2443 | 1002 | 41.0 | 0.4233 | 0.97 | (0.91, 1.04) | 0.95 | (0.85,1.07) | -0.01 | (-0.04, 0.02) | |
| Yes | 904 | 568 | 62.8 | 861 | 511 | 59.3 | 0.1336 | 0.94 | (0.88, 1.02) | 0.86 | (0.71,1.05) | -0.03 | (-0.08, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3139 |
| <130 | 1208 | 563 | 46.6 | 1190 | 512 | 43.0 | 0.0779 | 0.92 | (0.84, 1.01) | 0.87 | (0.74,1.02) | -0.04 | (-0.08, 0.00) | |
| >=130 | 2097 | 1017 | 48.5 | 2114 | 1001 | 47.4 | 0.4564 | 0.98 | (0.92, 1.04) | 0.96 | (0.85,1.08) | -0.01 | (-0.04, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9961 |
| <75 | 1286 | 697 | 54.2 | 1294 | 673 | 52.0 | 0.2651 | 0.96 | (0.89, 1.03) | 0.92 | (0.78,1.07) | -0.02 | (-0.06, 0.02) | |
| 75 to <85 | 1033 | 469 | 45.4 | 1019 | 443 | 43.5 | 0.3796 | 0.96 | (0.87, 1.05) | 0.92 | (0.78,1.10) | -0.02 | (-0.06, 0.02) | |
| >=85 | 986 | 414 | 42.0 | 991 | 397 | 40.1 | 0.3837 | 0.95 | (0.86, 1.06) | 0.92 | (0.77,1.10) | -0.02 | (-0.06, 0.02) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.1: 1 Proportion of patients with any adverse event occurring up to the final follow-up visit, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| History of heart failure | | | | | | | | | | | | | | 0.8717 |
| No | 2970 | 1349 | 45.4 | 2979 | 1299 | 43.6 | 0.1589 | 0.96 | (0.91, 1.02) | 0.93 | (0.84,1.03) | -0.02 | (-0.04, 0.01) | |
| Yes | 334 | 231 | 69.2 | 324 | 213 | 65.7 | 0.3490 | 0.95 | (0.85, 1.06) | 0.86 | (0.62,1.19) | -0.03 | (-0.11, 0.04) | |
| History of renal disease | | | | | | | | | | | | | | 0.4507 |
| Diabetic kidney disease | 1025 | 574 | 56.0 | 1032 | 550 | 53.3 | 0.2178 | 0.95 | (0.88, 1.03) | 0.90 | (0.75,1.07) | -0.03 | (-0.07, 0.02) | |
| Glomerular disease | 816 | 300 | 36.8 | 853 | 278 | 32.6 | 0.0732 | 0.89 | (0.78, 1.01) | 0.83 | (0.68,1.02) | -0.04 | (-0.09, 0.00) | |
| Hypertensive/renovascular disease | 739 | 348 | 47.1 | 706 | 330 | 46.7 | 0.8945 | 0.99 | (0.89, 1.11) | 0.99 | (0.80,1.21) | 0.00 | (-0.05, 0.05) | |
| Other/Unknown | 725 | 358 | 49.4 | 713 | 355 | 49.8 | 0.8764 | 1.01 | (0.91, 1.12) | 1.02 | (0.83,1.25) | 0.00 | (-0.05, 0.06) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4187 |
| <30 | 1151 | 632 | 54.9 | 1131 | 603 | 53.3 | 0.4451 | 0.97 | (0.90, 1.05) | 0.94 | (0.80,1.11) | -0.02 | (-0.06, 0.02) | |
| 30 to <45 | 1461 | 701 | 48.0 | 1467 | 652 | 44.4 | 0.0550 | 0.93 | (0.86,>1.00) | 0.87 | (0.75,1.00) | -0.04 | (-0.07, 0.00) | |
| >=45 | 693 | 247 | 35.6 | 706 | 258 | 36.5 | 0.7255 | 1.03 | (0.89, 1.18) | 1.04 | (0.84,1.29) | 0.01 | (-0.04, 0.06) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7463 |
| Normal (<30) | 663 | 345 | 52.0 | 665 | 326 | 49.0 | 0.2721 | 0.94 | (0.85, 1.05) | 0.89 | (0.71,1.10) | -0.03 | (-0.08, 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 468 | 49.9 | 927 | 434 | 46.8 | 0.1765 | 0.94 | (0.85, 1.03) | 0.88 | (0.74,1.06) | -0.03 | (-0.08, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 767 | 45.0 | 1712 | 753 | 44.0 | 0.5558 | 0.98 | (0.91, 1.05) | 0.96 | (0.84,1.10) | -0.01 | (-0.04, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9296 |
| Low, moderate or high | 833 | 357 | 42.9 | 839 | 343 | 40.9 | 0.4131 | 0.95 | (0.85, 1.07) | 0.92 | (0.76,1.12) | -0.02 | (-0.07, 0.03) | |
| Very high | 2472 | 1223 | 49.5 | 2465 | 1170 | 47.5 | 0.1577 | 0.96 | (0.91, 1.02) | 0.92 | (0.83,1.03) | -0.02 | (-0.05, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.6882 |
| No | 508 | 266 | 52.4 | 473 | 232 | 49.0 | 0.2996 | 0.94 | (0.83, 1.06) | 0.88 | (0.68,1.13) | -0.03 | (-0.10, 0.03) | |
| Yes | 2797 | 1314 | 47.0 | 2831 | 1281 | 45.2 | 0.1930 | 0.96 | (0.91, 1.02) | 0.93 | (0.84,1.04) | -0.02 | (-0.04, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9021 |
| No | 1940 | 821 | 42.3 | 1908 | 769 | 40.3 | 0.2042 | 0.95 | (0.88, 1.03) | 0.92 | (0.81,1.05) | -0.02 | (-0.05, 0.01) | |
| Yes | 1365 | 759 | 55.6 | 1396 | 744 | 53.3 | 0.2232 | 0.96 | (0.90, 1.03) | 0.91 | (0.78,1.06) | -0.02 | (-0.06, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2360 |
| No | 1852 | 722 | 39.0 | 1942 | 757 | 39.0 | 0.9978 | 1.00 | (0.92, 1.08) | 1.00 | (0.88,1.14) | 0.00 | (-0.03, 0.03) | |
| Yes | 1453 | 858 | 59.1 | 1362 | 756 | 55.5 | 0.0575 | 0.94 | (0.88,>1.00) | 0.87 | (0.74,1.00) | -0.04 | (-0.07, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the final follow-up visit, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 1488 | 45.0 | 3304 | 1424 | 43.1 | 0.1153 | 0.96 | (0.91,1.01) | 0.92 | (0.84,1.02) | -0.02 | (-0.04, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0416 |
| Male | 2210 | 996 | 45.1 | 2207 | 990 | 44.9 | 0.8881 | 1.00 | (0.93,1.06) | 0.99 | (0.88,1.12) | 0.00 | (-0.03, 0.03) | |
| Female | 1095 | 492 | 44.9 | 1097 | 434 | 39.6 | 0.0109 | 0.88 | (0.80,0.97) | 0.80 | (0.68,0.95) | -0.05 | (-0.09,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.9988 |
| <65 | 1501 | 563 | 37.5 | 1501 | 539 | 35.9 | 0.3635 | 0.96 | (0.87,1.05) | 0.93 | (0.80,1.08) | -0.02 | (-0.05, 0.02) | |
| >=65 | 1804 | 925 | 51.3 | 1803 | 885 | 49.1 | 0.1884 | 0.96 | (0.90,1.02) | 0.92 | (0.80,1.04) | -0.02 | (-0.05, 0.01) | |
| Region | | | | | | | | | | | | | | 0.2301 |
| North America | 873 | 425 | 48.7 | 844 | 363 | 43.0 | 0.0184 | 0.88 | (0.80,0.98) | 0.80 | (0.66,0.96) | -0.06 | (-0.10,-0.01) | |
| Europe | 1304 | 683 | 52.4 | 1344 | 701 | 52.2 | 0.9100 | 1.00 | (0.93,1.07) | 0.99 | (0.85,1.15) | 0.00 | (-0.04, 0.04) | |
| Japan | 308 | 111 | 36.0 | 304 | 114 | 37.5 | 0.7078 | 1.04 | (0.85,1.28) | 1.06 | (0.77,1.48) | 0.01 | (-0.06, 0.09) | |
| Other Asia | 820 | 269 | 32.8 | 812 | 246 | 30.3 | 0.2754 | 0.92 | (0.80,1.07) | 0.89 | (0.72,1.10) | -0.03 | (-0.07, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9661 |
| Diabetic | 1515 | 806 | 53.2 | 1525 | 775 | 50.8 | 0.1888 | 0.96 | (0.89,1.02) | 0.91 | (0.79,1.05) | -0.02 | (-0.06, 0.01) | |
| Non-diabetic | 1790 | 682 | 38.1 | 1779 | 649 | 36.5 | 0.3172 | 0.96 | (0.88,1.04) | 0.93 | (0.81,1.07) | -0.02 | (-0.05, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8313 |
| <30 | 1961 | 786 | 40.1 | 1955 | 744 | 38.1 | 0.1940 | 0.95 | (0.88,1.03) | 0.92 | (0.81,1.04) | -0.02 | (-0.05, 0.01) | |
| >=30 | 1337 | 699 | 52.3 | 1340 | 673 | 50.2 | 0.2870 | 0.96 | (0.89,1.03) | 0.92 | (0.79,1.07) | -0.02 | (-0.06, 0.02) | |
| Prior CV disease | | | | | | | | | | | | | | 0.4700 |
| No | 2401 | 954 | 39.7 | 2443 | 947 | 38.8 | 0.4896 | 0.98 | (0.91,1.05) | 0.96 | (0.86,1.08) | -0.01 | (-0.04, 0.02) | |
| Yes | 904 | 534 | 59.1 | 861 | 477 | 55.4 | 0.1192 | 0.94 | (0.87,1.02) | 0.86 | (0.71,1.04) | -0.04 | (-0.08, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2745 |
| <130 | 1208 | 531 | 44.0 | 1190 | 480 | 40.3 | 0.0726 | 0.92 | (0.84,1.01) | 0.86 | (0.73,1.01) | -0.04 | (-0.08, 0.00) | |
| >=130 | 2097 | 957 | 45.6 | 2114 | 944 | 44.7 | 0.5220 | 0.98 | (0.92,1.05) | 0.96 | (0.85,1.09) | -0.01 | (-0.04, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9185 |
| <75 | 1286 | 657 | 51.1 | 1294 | 635 | 49.1 | 0.3058 | 0.96 | (0.89,1.04) | 0.92 | (0.79,1.08) | -0.02 | (-0.06, 0.02) | |
| 75 to <85 | 1033 | 443 | 42.9 | 1019 | 411 | 40.3 | 0.2411 | 0.94 | (0.85,1.04) | 0.90 | (0.76,1.07) | -0.03 | (-0.07, 0.02) | |
| >=85 | 986 | 388 | 39.4 | 991 | 378 | 38.1 | 0.5816 | 0.97 | (0.87,1.08) | 0.95 | (0.79,1.14) | -0.01 | (-0.06, 0.03) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
Disease-related events are defined as all events from the SOC 'Cardiac Disorders' and the SOC 'Renal and urinary disorders'.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the final follow-up visit, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| History of heart failure | | | | | | | | | | | | | | 0.7506 |
| No | 2970 | 1271 | 42.8 | 2979 | 1225 | 41.1 | 0.1910 | 0.96 | (0.91,1.02) | 0.93 | (0.84,1.03) | -0.02 | (-0.04, 0.01) | |
| Yes | 334 | 217 | 65.0 | 324 | 198 | 61.1 | 0.3052 | 0.94 | (0.84,1.06) | 0.85 | (0.62,1.16) | -0.04 | (-0.11, 0.04) | |
| History of renal disease | | | | | | | | | | | | | | 0.4814 |
| Diabetic kidney disease | 1025 | 536 | 52.3 | 1032 | 516 | 50.0 | 0.2983 | 0.96 | (0.88,1.04) | 0.91 | (0.77,1.08) | -0.02 | (-0.07, 0.02) | |
| Glomerular disease | 816 | 281 | 34.4 | 853 | 259 | 30.4 | 0.0754 | 0.88 | (0.77,1.01) | 0.83 | (0.68,1.02) | -0.04 | (-0.09, 0.00) | |
| Hypertensive/renovascular disease | 739 | 326 | 44.1 | 706 | 306 | 43.3 | 0.7678 | 0.98 | (0.87,1.10) | 0.97 | (0.79,1.19) | -0.01 | (-0.06, 0.04) | |
| Other/Unknown | 725 | 345 | 47.6 | 713 | 343 | 48.1 | 0.8434 | 1.01 | (0.91,1.13) | 1.02 | (0.83,1.26) | 0.01 | (-0.05, 0.06) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5511 |
| <30 | 1151 | 590 | 51.3 | 1131 | 560 | 49.5 | 0.4042 | 0.97 | (0.89,1.05) | 0.93 | (0.79,1.10) | -0.02 | (-0.06, 0.02) | |
| 30 to <45 | 1461 | 663 | 45.4 | 1467 | 620 | 42.3 | 0.0892 | 0.93 | (0.86,1.01) | 0.88 | (0.76,1.02) | -0.03 | (-0.07, 0.00) | |
| >=45 | 693 | 235 | 33.9 | 706 | 244 | 34.6 | 0.7977 | 1.02 | (0.88,1.18) | 1.03 | (0.83,1.28) | 0.01 | (-0.04, 0.06) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8225 |
| Normal (<30) | 663 | 331 | 49.9 | 665 | 308 | 46.3 | 0.1882 | 0.93 | (0.83,1.04) | 0.87 | (0.70,1.07) | -0.04 | (-0.09, 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 438 | 46.7 | 927 | 417 | 45.0 | 0.4455 | 0.96 | (0.87,1.06) | 0.93 | (0.78,1.12) | -0.02 | (-0.06, 0.03) | |
| Macroalbuminuria (>300) | 1705 | 719 | 42.2 | 1712 | 699 | 40.8 | 0.4265 | 0.97 | (0.89,1.05) | 0.95 | (0.83,1.08) | -0.01 | (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9952 |
| Low, moderate or high | 833 | 340 | 40.8 | 839 | 328 | 39.1 | 0.4722 | 0.96 | (0.85,1.08) | 0.93 | (0.77,1.13) | -0.02 | (-0.06, 0.03) | |
| Very high | 2472 | 1148 | 46.4 | 2465 | 1096 | 44.5 | 0.1629 | 0.96 | (0.90,1.02) | 0.92 | (0.83,1.03) | -0.02 | (-0.05, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.6473 |
| No | 508 | 248 | 48.8 | 473 | 215 | 45.5 | 0.2915 | 0.93 | (0.82,1.06) | 0.87 | (0.68,1.12) | -0.03 | (-0.10, 0.03) | |
| Yes | 2797 | 1240 | 44.3 | 2831 | 1209 | 42.7 | 0.2182 | 0.96 | (0.91,1.02) | 0.94 | (0.84,1.04) | -0.02 | (-0.04, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6583 |
| No | 1940 | 778 | 40.1 | 1908 | 722 | 37.8 | 0.1502 | 0.94 | (0.87,1.02) | 0.91 | (0.80,1.04) | -0.02 | (-0.05, 0.01) | |
| Yes | 1365 | 710 | 52.0 | 1396 | 702 | 50.3 | 0.3638 | 0.97 | (0.90,1.04) | 0.93 | (0.80,1.08) | -0.02 | (-0.05, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3968 |
| No | 1852 | 684 | 36.9 | 1942 | 711 | 36.6 | 0.8374 | 0.99 | (0.91,1.08) | 0.99 | (0.86,1.13) | 0.00 | (-0.03, 0.03) | |
| Yes | 1453 | 804 | 55.3 | 1362 | 713 | 52.3 | 0.1124 | 0.95 | (0.88,1.01) | 0.89 | (0.76,1.03) | -0.03 | (-0.07, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
Disease-related events are defined as all events from the SOC 'Cardiac Disorders' and the SOC 'Renal and urinary disorders'.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.1: 3 Proportion of patients with serious adverse events occurring up to the final follow-up visit, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 1245 | 37.7 | 3304 | 1164 | 35.2 | 0.0393 | 0.94 | (0.88,<1.00) | 0.90 | (0.81,0.99) | -0.02 | (-0.05, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4530 |
| Male | 2210 | 838 | 37.9 | 2207 | 796 | 36.1 | 0.2025 | 0.95 | (0.88, 1.03) | 0.92 | (0.82,1.04) | -0.02 | (-0.05, 0.01) | |
| Female | 1095 | 407 | 37.2 | 1097 | 368 | 33.5 | 0.0761 | 0.90 | (0.81, 1.01) | 0.85 | (0.72,1.02) | -0.04 | (-0.08, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.1989 |
| <65 | 1501 | 429 | 28.6 | 1501 | 425 | 28.3 | 0.8715 | 0.99 | (0.88, 1.11) | 0.99 | (0.84,1.16) | 0.00 | (-0.03, 0.03) | |
| >=65 | 1804 | 816 | 45.2 | 1803 | 739 | 41.0 | 0.0100 | 0.91 | (0.84, 0.98) | 0.84 | (0.74,0.96) | -0.04 | (-0.07,-0.01) | |
| Region | | | | | | | | | | | | | | 0.6057 |
| North America | 873 | 339 | 38.8 | 844 | 285 | 33.8 | 0.0292 | 0.87 | (0.77, 0.99) | 0.80 | (0.66,0.98) | -0.05 | (-0.10,-0.01) | |
| Europe | 1304 | 567 | 43.5 | 1344 | 562 | 41.8 | 0.3861 | 0.96 | (0.88, 1.05) | 0.93 | (0.80,1.09) | -0.02 | (-0.05, 0.02) | |
| Japan | 308 | 99 | 32.1 | 304 | 96 | 31.6 | 0.8810 | 0.98 | (0.78, 1.24) | 0.97 | (0.69,1.37) | -0.01 | (-0.08, 0.07) | |
| Other Asia | 820 | 240 | 29.3 | 812 | 221 | 27.2 | 0.3573 | 0.93 | (0.80, 1.09) | 0.90 | (0.73,1.12) | -0.02 | (-0.06, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4018 |
| Diabetic | 1515 | 705 | 46.5 | 1525 | 647 | 42.4 | 0.0227 | 0.91 | (0.84, 0.99) | 0.85 | (0.73,0.98) | -0.04 | (-0.08,-0.01) | |
| Non-diabetic | 1790 | 540 | 30.2 | 1779 | 517 | 29.1 | 0.4692 | 0.96 | (0.87, 1.07) | 0.95 | (0.82,1.09) | -0.01 | (-0.04, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6998 |
| <30 | 1961 | 670 | 34.2 | 1955 | 616 | 31.5 | 0.0767 | 0.92 | (0.84, 1.01) | 0.89 | (0.78,1.01) | -0.03 | (-0.06, 0.00) | |
| >=30 | 1337 | 573 | 42.9 | 1340 | 543 | 40.5 | 0.2206 | 0.95 | (0.86, 1.03) | 0.91 | (0.78,1.06) | -0.02 | (-0.06, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | 0.1121 |
| No | 2401 | 759 | 31.6 | 2443 | 755 | 30.9 | 0.5955 | 0.98 | (0.90, 1.06) | 0.97 | (0.86,1.09) | -0.01 | (-0.03, 0.02) | |
| Yes | 904 | 486 | 53.8 | 861 | 409 | 47.5 | 0.0086 | 0.88 | (0.81, 0.97) | 0.78 | (0.65,0.94) | -0.06 | (-0.11,-0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8232 |
| <130 | 1208 | 430 | 35.6 | 1190 | 400 | 33.6 | 0.3076 | 0.94 | (0.85, 1.05) | 0.92 | (0.77,1.08) | -0.02 | (-0.06, 0.02) | |
| >=130 | 2097 | 815 | 38.9 | 2114 | 764 | 36.1 | 0.0678 | 0.93 | (0.86, 1.01) | 0.89 | (0.79,1.01) | -0.03 | (-0.06, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8563 |
| <75 | 1286 | 566 | 44.0 | 1294 | 529 | 40.9 | 0.1076 | 0.93 | (0.85, 1.02) | 0.88 | (0.75,1.03) | -0.03 | (-0.07, 0.01) | |
| 75 to <85 | 1033 | 349 | 33.8 | 1019 | 331 | 32.5 | 0.5309 | 0.96 | (0.85, 1.09) | 0.94 | (0.78,1.13) | -0.01 | (-0.05, 0.03) | |
| >=85 | 986 | 330 | 33.5 | 991 | 304 | 30.7 | 0.1835 | 0.92 | (0.81, 1.04) | 0.88 | (0.73,1.06) | -0.03 | (-0.07, 0.01) | |

Analyses are based on 1245.137.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.1: 3 Proportion of patients with serious adverse events occurring up to the final follow-up visit, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| History of heart failure | | | | | | | | | | | | | | 0.3836 |
| No | 2970 | 1039 | 35.0 | 2979 | 986 | 33.1 | 0.1250 | 0.95 | (0.88, 1.02) | 0.92 | (0.83,1.02) | -0.02 | (-0.04, 0.01) | |
| Yes | 334 | 206 | 61.7 | 324 | 177 | 54.6 | 0.0669 | 0.89 | (0.78, 1.01) | 0.75 | (0.55,1.02) | -0.07 | (-0.15, 0.00) | |
| History of renal disease | | | | | | | | | | | | | | 0.1277 |
| Diabetic kidney disease | 1025 | 469 | 45.8 | 1032 | 426 | 41.3 | 0.0406 | 0.90 | (0.82,<1.00) | 0.83 | (0.70,0.99) | -0.04 | (-0.09, 0.00) | |
| Glomerular disease | 816 | 227 | 27.8 | 853 | 197 | 23.1 | 0.0267 | 0.83 | (0.70, 0.98) | 0.78 | (0.62,0.97) | -0.05 | (-0.09,-0.01) | |
| Hypertensive/renovascular disease | 739 | 274 | 37.1 | 706 | 261 | 37.0 | 0.9660 | 1.00 | (0.87, 1.14) | 1.00 | (0.80,1.23) | 0.00 | (-0.05, 0.05) | |
| Other/Unknown | 725 | 275 | 37.9 | 713 | 280 | 39.3 | 0.6018 | 1.04 | (0.91, 1.18) | 1.06 | (0.86,1.31) | 0.01 | (-0.04, 0.06) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4355 |
| <30 | 1151 | 523 | 45.4 | 1131 | 483 | 42.7 | 0.1886 | 0.94 | (0.86, 1.03) | 0.90 | (0.76,1.06) | -0.03 | (-0.07, 0.01) | |
| 30 to <45 | 1461 | 540 | 37.0 | 1467 | 490 | 33.4 | 0.0437 | 0.90 | (0.82,<1.00) | 0.86 | (0.73,1.00) | -0.04 | (-0.07, 0.00) | |
| >=45 | 693 | 182 | 26.3 | 706 | 191 | 27.1 | 0.7379 | 1.03 | (0.87, 1.23) | 1.04 | (0.82,1.32) | 0.01 | (-0.04, 0.05) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8377 |
| Normal (<30) | 663 | 266 | 40.1 | 665 | 244 | 36.7 | 0.1989 | 0.91 | (0.80, 1.05) | 0.87 | (0.69,1.08) | -0.03 | (-0.09, 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 367 | 39.2 | 927 | 334 | 36.0 | 0.1621 | 0.92 | (0.82, 1.03) | 0.87 | (0.73,1.06) | -0.03 | (-0.08, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 612 | 35.9 | 1712 | 586 | 34.2 | 0.3077 | 0.95 | (0.87, 1.04) | 0.93 | (0.81,1.07) | -0.02 | (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7817 |
| Low, moderate or high | 833 | 268 | 32.2 | 839 | 257 | 30.6 | 0.4972 | 0.95 | (0.83, 1.10) | 0.93 | (0.76,1.14) | -0.02 | (-0.06, 0.03) | |
| Very high | 2472 | 977 | 39.5 | 2465 | 907 | 36.8 | 0.0485 | 0.93 | (0.87,<1.00) | 0.89 | (0.79,1.00) | -0.03 | (-0.05, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.3089 |
| No | 508 | 231 | 45.5 | 473 | 188 | 39.7 | 0.0700 | 0.87 | (0.76, 1.01) | 0.79 | (0.61,1.02) | -0.06 | (-0.12, 0.00) | |
| Yes | 2797 | 1014 | 36.3 | 2831 | 976 | 34.5 | 0.1631 | 0.95 | (0.89, 1.02) | 0.93 | (0.83,1.03) | -0.02 | (-0.04, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3256 |
| No | 1940 | 616 | 31.8 | 1908 | 583 | 30.6 | 0.4228 | 0.96 | (0.88, 1.06) | 0.95 | (0.83,1.08) | -0.01 | (-0.04, 0.02) | |
| Yes | 1365 | 629 | 46.1 | 1396 | 581 | 41.6 | 0.0182 | 0.90 | (0.83, 0.98) | 0.83 | (0.72,0.97) | -0.04 | (-0.08,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2056 |
| No | 1852 | 558 | 30.1 | 1942 | 578 | 29.8 | 0.8054 | 0.99 | (0.90, 1.09) | 0.98 | (0.86,1.13) | 0.00 | (-0.03, 0.03) | |
| Yes | 1453 | 687 | 47.3 | 1362 | 586 | 43.0 | 0.0234 | 0.91 | (0.84, 0.99) | 0.84 | (0.73,0.98) | -0.04 | (-0.08,-0.01) | |

Analyses are based on 1245.137.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the final follow-up visit, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 1131 | 34.2 | 3304 | 1044 | 31.6 | 0.0233 | 0.92 | (0.86, 0.99) | 0.89 | (0.80,0.98) | -0.03 | (-0.05, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.2733 |
| Male | 2210 | 756 | 34.2 | 2207 | 716 | 32.4 | 0.2132 | 0.95 | (0.87, 1.03) | 0.92 | (0.81,1.05) | -0.02 | (-0.05, 0.01) | |
| Female | 1095 | 375 | 34.2 | 1097 | 328 | 29.9 | 0.0292 | 0.87 | (0.77, 0.99) | 0.82 | (0.68,0.98) | -0.04 | (-0.08, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.4425 |
| <65 | 1501 | 388 | 25.8 | 1501 | 372 | 24.8 | 0.5018 | 0.96 | (0.85, 1.08) | 0.95 | (0.80,1.11) | -0.01 | (-0.04, 0.02) | |
| >=65 | 1804 | 743 | 41.2 | 1803 | 672 | 37.3 | 0.0160 | 0.90 | (0.83, 0.98) | 0.85 | (0.74,0.97) | -0.04 | (-0.07,-0.01) | |
| Region | | | | | | | | | | | | | | 0.8154 |
| North America | 873 | 305 | 34.9 | 844 | 260 | 30.8 | 0.0685 | 0.88 | (0.77, 1.01) | 0.83 | (0.68,1.01) | -0.04 | (-0.09, 0.00) | |
| Europe | 1304 | 529 | 40.6 | 1344 | 513 | 38.2 | 0.2067 | 0.94 | (0.86, 1.03) | 0.90 | (0.77,1.06) | -0.02 | (-0.06, 0.01) | |
| Japan | 308 | 93 | 30.2 | 304 | 90 | 29.6 | 0.8735 | 0.98 | (0.77, 1.25) | 0.97 | (0.69,1.37) | -0.01 | (-0.08, 0.07) | |
| Other Asia | 820 | 204 | 24.9 | 812 | 181 | 22.3 | 0.2183 | 0.90 | (0.75, 1.07) | 0.87 | (0.69,1.09) | -0.03 | (-0.07, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3795 |
| Diabetic | 1515 | 640 | 42.2 | 1525 | 578 | 37.9 | 0.0146 | 0.90 | (0.82, 0.98) | 0.83 | (0.72,0.96) | -0.04 | (-0.08,-0.01) | |
| Non-diabetic | 1790 | 491 | 27.4 | 1779 | 466 | 26.2 | 0.4047 | 0.95 | (0.86, 1.06) | 0.94 | (0.81,1.09) | -0.01 | (-0.04, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8375 |
| <30 | 1961 | 601 | 30.6 | 1955 | 548 | 28.0 | 0.0721 | 0.91 | (0.83, 1.01) | 0.88 | (0.77,1.01) | -0.03 | (-0.05, 0.00) | |
| >=30 | 1337 | 528 | 39.5 | 1340 | 491 | 36.6 | 0.1289 | 0.93 | (0.84, 1.02) | 0.89 | (0.76,1.04) | -0.03 | (-0.07, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | 0.0539 |
| No | 2401 | 685 | 28.5 | 2443 | 681 | 27.9 | 0.6129 | 0.98 | (0.89, 1.07) | 0.97 | (0.85,1.10) | -0.01 | (-0.03, 0.02) | |
| Yes | 904 | 446 | 49.3 | 861 | 363 | 42.2 | 0.0025 | 0.85 | (0.77, 0.95) | 0.75 | (0.62,0.90) | -0.07 | (-0.12,-0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6847 |
| <130 | 1208 | 386 | 32.0 | 1190 | 358 | 30.1 | 0.3224 | 0.94 | (0.84, 1.06) | 0.92 | (0.77,1.09) | -0.02 | (-0.06, 0.02) | |
| >=130 | 2097 | 745 | 35.5 | 2114 | 686 | 32.5 | 0.0351 | 0.91 | (0.84, 0.99) | 0.87 | (0.77,0.99) | -0.03 | (-0.06, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9925 |
| <75 | 1286 | 515 | 40.0 | 1294 | 476 | 36.8 | 0.0886 | 0.92 | (0.83, 1.01) | 0.87 | (0.74,1.02) | -0.03 | (-0.07, 0.00) | |
| 75 to <85 | 1033 | 317 | 30.7 | 1019 | 290 | 28.5 | 0.2689 | 0.93 | (0.81, 1.06) | 0.90 | (0.74,1.09) | -0.02 | (-0.06, 0.02) | |
| >=85 | 986 | 299 | 30.3 | 991 | 278 | 28.1 | 0.2665 | 0.93 | (0.81, 1.06) | 0.90 | (0.74,1.09) | -0.02 | (-0.06, 0.02) | |

Analyses are based on 1245.137. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
Disease-related events are defined as all events from the SOC 'Cardiac Disorders' and the SOC 'Renal and urinary disorders'.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the final follow-up visit, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| History of heart failure | | | | | | | | | | | | | | 0.2774 |
| No | 2970 | 943 | 31.8 | 2979 | 887 | 29.8 | 0.0987 | 0.94 | (0.87, 1.01) | 0.91 | (0.82,1.02) | -0.02 | (-0.04, 0.00) | |
| Yes | 334 | 188 | 56.3 | 324 | 156 | 48.1 | 0.0366 | 0.86 | (0.74, 0.99) | 0.72 | (0.53,0.98) | -0.08 | (-0.16,-0.01) | |
| History of renal disease | | | | | | | | | | | | | | 0.1609 |
| Diabetic kidney disease | 1025 | 421 | 41.1 | 1032 | 378 | 36.6 | 0.0386 | 0.89 | (0.80, 0.99) | 0.83 | (0.69,0.99) | -0.04 | (-0.09, 0.00) | |
| Glomerular disease | 816 | 202 | 24.8 | 853 | 172 | 20.2 | 0.0246 | 0.81 | (0.68, 0.97) | 0.77 | (0.61,0.97) | -0.05 | (-0.09,-0.01) | |
| Hypertensive/renovascular disease | 739 | 249 | 33.7 | 706 | 232 | 32.9 | 0.7370 | 0.98 | (0.84, 1.13) | 0.96 | (0.77,1.20) | -0.01 | (-0.06, 0.04) | |
| Other/Unknown | 725 | 259 | 35.7 | 713 | 262 | 36.7 | 0.6869 | 1.03 | (0.90, 1.18) | 1.05 | (0.84,1.30) | 0.01 | (-0.04, 0.06) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4863 |
| <30 | 1151 | 471 | 40.9 | 1131 | 425 | 37.6 | 0.1020 | 0.92 | (0.83, 1.02) | 0.87 | (0.73,1.03) | -0.03 | (-0.07, 0.01) | |
| 30 to <45 | 1461 | 492 | 33.7 | 1467 | 444 | 30.3 | 0.0479 | 0.90 | (0.81,<1.00) | 0.85 | (0.73,1.00) | -0.03 | (-0.07, 0.00) | |
| >=45 | 693 | 168 | 24.2 | 706 | 175 | 24.8 | 0.8127 | 1.02 | (0.85, 1.23) | 1.03 | (0.81,1.31) | 0.01 | (-0.04, 0.05) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8045 |
| Normal (<30) | 663 | 247 | 37.3 | 665 | 219 | 32.9 | 0.0989 | 0.88 | (0.76, 1.02) | 0.83 | (0.66,1.04) | -0.04 | (-0.09, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 330 | 35.2 | 927 | 306 | 33.0 | 0.3145 | 0.94 | (0.83, 1.06) | 0.91 | (0.75,1.10) | -0.02 | (-0.07, 0.02) | |
| Macroalbuminuria (>300) | 1705 | 554 | 32.5 | 1712 | 519 | 30.3 | 0.1703 | 0.93 | (0.84, 1.03) | 0.90 | (0.78,1.04) | -0.02 | (-0.05, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5192 |
| Low, moderate or high | 833 | 245 | 29.4 | 839 | 238 | 28.4 | 0.6375 | 0.96 | (0.83, 1.12) | 0.95 | (0.77,1.17) | -0.01 | (-0.05, 0.03) | |
| Very high | 2472 | 886 | 35.8 | 2465 | 806 | 32.7 | 0.0200 | 0.91 | (0.84, 0.99) | 0.87 | (0.77,0.98) | -0.03 | (-0.06, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.2257 |
| No | 508 | 211 | 41.5 | 473 | 166 | 35.1 | 0.0383 | 0.84 | (0.72, 0.99) | 0.76 | (0.59,0.99) | -0.06 | (-0.13, 0.00) | |
| Yes | 2797 | 920 | 32.9 | 2831 | 878 | 31.0 | 0.1307 | 0.94 | (0.87, 1.02) | 0.92 | (0.82,1.03) | -0.02 | (-0.04, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5932 |
| No | 1940 | 566 | 29.2 | 1908 | 522 | 27.4 | 0.2108 | 0.94 | (0.85, 1.04) | 0.91 | (0.79,1.05) | -0.02 | (-0.05, 0.01) | |
| Yes | 1365 | 565 | 41.4 | 1396 | 522 | 37.4 | 0.0315 | 0.90 | (0.82, 0.99) | 0.85 | (0.73,0.99) | -0.04 | (-0.08, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3204 |
| No | 1852 | 511 | 27.6 | 1942 | 519 | 26.7 | 0.5485 | 0.97 | (0.87, 1.08) | 0.96 | (0.83,1.10) | -0.01 | (-0.04, 0.02) | |
| Yes | 1453 | 620 | 42.7 | 1362 | 525 | 38.5 | 0.0260 | 0.90 | (0.83, 0.99) | 0.84 | (0.72,0.98) | -0.04 | (-0.08, 0.00) | |

Analyses are based on 1245.137. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
Disease-related events are defined as all events from the SOC 'Cardiac Disorders' and the SOC 'Renal and urinary disorders'.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

R.1.2.2 Adverse events leading to treatment discontinuation

Table R.1.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation occurring up to the final follow-up visit, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 247 | 7.5 | 3304 | 235 | 7.1 | 0.5726 | 0.95 | (0.80, 1.13) | 0.95 | (0.79,1.14) | 0.00 | (-0.02,0.01) | |
| Sex | | | | | | | | | | | | | | 0.4277 |
| Male | 2210 | 171 | 7.7 | 2207 | 170 | 7.7 | 0.9654 | 1.00 | (0.81, 1.22) | 1.00 | (0.80,1.24) | 0.00 | (-0.02,0.02) | |
| Female | 1095 | 76 | 6.9 | 1097 | 65 | 5.9 | 0.3326 | 0.85 | (0.62, 1.18) | 0.84 | (0.60,1.19) | -0.01 | (-0.03,0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.2362 |
| <65 | 1501 | 63 | 4.2 | 1501 | 71 | 4.7 | 0.4795 | 1.13 | (0.81, 1.57) | 1.13 | (0.80,1.60) | 0.01 | (-0.01,0.02) | |
| >=65 | 1804 | 184 | 10.2 | 1803 | 164 | 9.1 | 0.2617 | 0.89 | (0.73, 1.09) | 0.88 | (0.71,1.10) | -0.01 | (-0.03,0.01) | |
| Region | | | | | | | | | | | | | | 0.3988 |
| North America | 873 | 80 | 9.2 | 844 | 67 | 7.9 | 0.3643 | 0.87 | (0.64, 1.18) | 0.85 | (0.61,1.20) | -0.01 | (-0.04,0.01) | |
| Europe | 1304 | 111 | 8.5 | 1344 | 123 | 9.2 | 0.5621 | 1.08 | (0.84, 1.37) | 1.08 | (0.83,1.42) | 0.01 | (-0.02,0.03) | |
| Japan | 308 | 16 | 5.2 | 304 | 17 | 5.6 | 0.8278 | 1.08 | (0.55, 2.09) | 1.08 | (0.54,2.18) | 0.00 | (-0.03,0.04) | |
| Other Asia | 820 | 40 | 4.9 | 812 | 28 | 3.4 | 0.1484 | 0.71 | (0.44, 1.13) | 0.70 | (0.43,1.14) | -0.01 | (-0.03,0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0754 |
| Diabetic | 1515 | 161 | 10.6 | 1525 | 136 | 8.9 | 0.1125 | 0.84 | (0.68, 1.04) | 0.82 | (0.65,1.05) | -0.02 | (-0.04,0.00) | |
| Non-diabetic | 1790 | 86 | 4.8 | 1779 | 99 | 5.6 | 0.3055 | 1.16 | (0.87, 1.53) | 1.17 | (0.87,1.57) | 0.01 | (-0.01,0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4950 |
| <30 | 1961 | 127 | 6.5 | 1955 | 127 | 6.5 | 0.9799 | 1.00 | (0.79, 1.27) | 1.00 | (0.78,1.29) | 0.00 | (-0.02,0.02) | |
| >=30 | 1337 | 120 | 9.0 | 1340 | 107 | 8.0 | 0.3578 | 0.89 | (0.69, 1.14) | 0.88 | (0.67,1.16) | -0.01 | (-0.03,0.01) | |
| Prior CV disease | | | | | | | | | | | | | | 0.9124 |
| No | 2401 | 138 | 5.7 | 2443 | 134 | 5.5 | 0.6915 | 0.95 | (0.76, 1.20) | 0.95 | (0.75,1.22) | 0.00 | (-0.02,0.01) | |
| Yes | 904 | 109 | 12.1 | 861 | 101 | 11.7 | 0.8320 | 0.97 | (0.75, 1.25) | 0.97 | (0.73,1.29) | 0.00 | (-0.03,0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1832 |
| <130 | 1208 | 79 | 6.5 | 1190 | 87 | 7.3 | 0.4570 | 1.12 | (0.83, 1.50) | 1.13 | (0.82,1.55) | 0.01 | (-0.01,0.03) | |
| >=130 | 2097 | 168 | 8.0 | 2114 | 148 | 7.0 | 0.2133 | 0.87 | (0.71, 1.08) | 0.86 | (0.69,1.09) | -0.01 | (-0.03,0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5387 |
| <75 | 1286 | 121 | 9.4 | 1294 | 127 | 9.8 | 0.7268 | 1.04 | (0.82, 1.32) | 1.05 | (0.81,1.36) | 0.00 | (-0.02,0.03) | |
| 75 to <85 | 1033 | 71 | 6.9 | 1019 | 62 | 6.1 | 0.4681 | 0.89 | (0.64, 1.23) | 0.88 | (0.62,1.25) | -0.01 | (-0.03,0.01) | |
| >=85 | 986 | 55 | 5.6 | 991 | 46 | 4.6 | 0.3444 | 0.83 | (0.57, 1.22) | 0.82 | (0.55,1.23) | -0.01 | (-0.03,0.01) | |

Analyses are based on 1245.137.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation occurring up to the final follow-up visit, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| History of heart failure | | | | | | | | | | | | | | 0.1841 |
| No | 2970 | 203 | 6.8 | 2979 | 183 | 6.1 | 0.2786 | 0.90 | (0.74, 1.09) | 0.89 | (0.73,1.10) | -0.01 | (-0.02,0.01) | |
| Yes | 334 | 44 | 13.2 | 324 | 51 | 15.7 | 0.3489 | 1.19 | (0.82, 1.74) | 1.23 | (0.80,1.90) | 0.03 | (-0.03,0.08) | |
| History of renal disease | | | | | | | | | | | | | | 0.0170 |
| Diabetic kidney disease | 1025 | 120 | 11.7 | 1032 | 92 | 8.9 | 0.0373 | 0.76 | (0.59, 0.99) | 0.74 | (0.55,0.98) | -0.03 | (-0.05,0.00) | |
| Glomerular disease | 816 | 37 | 4.5 | 853 | 31 | 3.6 | 0.3525 | 0.80 | (0.50, 1.28) | 0.79 | (0.49,1.29) | -0.01 | (-0.03,0.01) | |
| Hypertensive/renovascular disease | 739 | 49 | 6.6 | 706 | 49 | 6.9 | 0.8148 | 1.05 | (0.71, 1.53) | 1.05 | (0.70,1.58) | 0.00 | (-0.02,0.03) | |
| Other/Unknown | 725 | 41 | 5.7 | 713 | 63 | 8.8 | 0.0199 | 1.56 | (1.07, 2.28) | 1.62 | (1.08,2.43) | 0.03 | ( 0.01,0.06) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9671 |
| <30 | 1151 | 122 | 10.6 | 1131 | 112 | 9.9 | 0.5833 | 0.93 | (0.73, 1.19) | 0.93 | (0.71,1.22) | -0.01 | (-0.03,0.02) | |
| 30 to <45 | 1461 | 102 | 7.0 | 1467 | 100 | 6.8 | 0.8603 | 0.98 | (0.75, 1.27) | 0.97 | (0.73,1.30) | 0.00 | (-0.02,0.02) | |
| >=45 | 693 | 23 | 3.3 | 706 | 23 | 3.3 | 0.9489 | 0.98 | (0.56, 1.73) | 0.98 | (0.55,1.77) | 0.00 | (-0.02,0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.0844 |
| Normal (<30) | 663 | 52 | 7.8 | 665 | 55 | 8.3 | 0.7747 | 1.05 | (0.73, 1.52) | 1.06 | (0.71,1.57) | 0.00 | (-0.02,0.03) | |
| Microalbuminuria (30 to <=300) | 937 | 65 | 6.9 | 927 | 78 | 8.4 | 0.2309 | 1.21 | (0.88, 1.66) | 1.23 | (0.88,1.74) | 0.01 | (-0.01,0.04) | |
| Macroalbuminuria (>300) | 1705 | 130 | 7.6 | 1712 | 102 | 6.0 | 0.0528 | 0.78 | (0.61,>1.00) | 0.77 | (0.59,1.00) | -0.02 | (-0.03,0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2295 |
| Low, moderate or high | 833 | 38 | 4.6 | 839 | 46 | 5.5 | 0.3887 | 1.20 | (0.79, 1.83) | 1.21 | (0.78,1.89) | 0.01 | (-0.01,0.03) | |
| Very high | 2472 | 209 | 8.5 | 2465 | 189 | 7.7 | 0.3096 | 0.91 | (0.75, 1.10) | 0.90 | (0.73,1.10) | -0.01 | (-0.02,0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.4930 |
| No | 508 | 59 | 11.6 | 473 | 47 | 9.9 | 0.3977 | 0.86 | (0.60, 1.23) | 0.84 | (0.56,1.26) | -0.02 | (-0.06,0.02) | |
| Yes | 2797 | 188 | 6.7 | 2831 | 188 | 6.6 | 0.9035 | 0.99 | (0.81, 1.20) | 0.99 | (0.80,1.22) | 0.00 | (-0.01,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8393 |
| No | 1940 | 116 | 6.0 | 1908 | 106 | 5.6 | 0.5729 | 0.93 | (0.72, 1.20) | 0.92 | (0.71,1.21) | 0.00 | (-0.02,0.01) | |
| Yes | 1365 | 131 | 9.6 | 1396 | 129 | 9.2 | 0.7485 | 0.96 | (0.76, 1.21) | 0.96 | (0.74,1.24) | 0.00 | (-0.03,0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3678 |
| No | 1852 | 92 | 5.0 | 1942 | 103 | 5.3 | 0.6392 | 1.07 | (0.81, 1.40) | 1.07 | (0.80,1.43) | 0.00 | (-0.01,0.02) | |
| Yes | 1453 | 155 | 10.7 | 1362 | 132 | 9.7 | 0.3924 | 0.91 | (0.73, 1.13) | 0.90 | (0.70,1.15) | -0.01 | (-0.03,0.01) | |

Analyses are based on 1245.137.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the final follow-up visit by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Number of patients | 3305 (100.0) | | | 3304 (100.0) | | |
| Total with adverse events | 247 ( 7.5) | 6331.90 | 3.90 | 235 ( 7.1) | 6339.41 | 3.71 |
| Infections and infestations | 53 ( 1.6) | 6462.74 | 0.82 | 61 ( 1.8) | 6457.76 | 0.94 |
| Corona virus infection | 21 ( 0.6) | 6482.57 | 0.32 | 18 ( 0.5) | 6494.72 | 0.28 |
| Urinary tract infection | 1 ( <0.1) | 6482.67 | 0.02 | 8 ( 0.2) | 6483.28 | 0.12 |
| Pneumonia | 8 ( 0.2) | 6484.54 | 0.12 | 6 ( 0.2) | 6495.31 | 0.09 |
| Diabetic foot infection | 0 | 6484.63 | 0 | 2 ( 0.1) | 6495.30 | 0.03 |
| Diverticulitis | 0 | 6484.63 | 0 | 2 ( 0.1) | 6492.78 | 0.03 |
| Genital infection fungal | 0 | 6484.63 | 0 | 2 ( 0.1) | 6492.27 | 0.03 |
| Penile infection | 0 | 6484.63 | 0 | 2 ( 0.1) | 6493.52 | 0.03 |
| Sepsis | 1 ( <0.1) | 6484.63 | 0.02 | 2 ( 0.1) | 6494.72 | 0.03 |
| Vulvovaginal candidiasis | 0 | 6484.63 | 0 | 2 ( 0.1) | 6490.56 | 0.03 |
| Balanitis candida | 2 ( 0.1) | 6480.43 | 0.03 | 0 | 6495.44 | 0 |
| Endocarditis | 2 ( 0.1) | 6484.51 | 0.03 | 0 | 6495.44 | 0 |
| Urosepsis | 2 ( 0.1) | 6483.14 | 0.03 | 0 | 6495.44 | 0 |
| Abdominal sepsis | 1 ( <0.1) | 6484.63 | 0.02 | 1 ( <0.1) | 6495.44 | 0.02 |
| Abscess | 0 | 6484.63 | 0 | 1 ( <0.1) | 6493.86 | 0.02 |
| Arthritis infective | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.36 | 0.02 |
| Candida infection | 1 ( <0.1) | 6483.59 | 0.02 | 1 ( <0.1) | 6492.86 | 0.02 |
| Genital candidiasis | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.63 | 0.02 |
| Genital infection male | 1 ( <0.1) | 6482.67 | 0.02 | 1 ( <0.1) | 6494.22 | 0.02 |
| Haematoma infection | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.40 | 0.02 |
| Joint abscess | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.80 | 0.02 |
| Necrotising soft tissue infection | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.36 | 0.02 |
| Pneumonia bacterial | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.42 | 0.02 |
| Septic shock | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.36 | 0.02 |
| Soft tissue infection | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.36 | 0.02 |
| Urethritis | 0 | 6484.63 | 0 | 1 ( <0.1) | 6492.64 | 0.02 |
| Urinary tract infection bacterial | 1 ( <0.1) | 6484.26 | 0.02 | 1 ( <0.1) | 6495.40 | 0.02 |
| Viral infection | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.24 | 0.02 |
| Vulvovaginitis | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.48 | 0.02 |
| Wound sepsis | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.44 | 0.02 |
| Abdominal abscess | 1 ( <0.1) | 6484.52 | 0.02 | 0 | 6495.44 | 0 |
| Bacterial infection | 1 ( <0.1) | 6483.50 | 0.02 | 0 | 6495.44 | 0 |
| Cellulitis | 1 ( <0.1) | 6484.63 | 0.02 | 0 | 6495.44 | 0 |
| Endocarditis bacterial | 1 ( <0.1) | 6484.55 | 0.02 | 0 | 6495.44 | 0 |
| Fungal balanitis | 1 ( <0.1) | 6482.25 | 0.02 | 0 | 6495.44 | 0 |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 20.1

Table R.1.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the final follow-up visit by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Infections and infestations (cont.) | | | | | | |
| Gastroenteritis | 1 ( <0.1) | 6482.78 | 0.02 | 0 | 6495.44 | 0 |
| Meningoencephalitis bacterial | 1 ( <0.1) | 6484.61 | 0.02 | 0 | 6495.44 | 0 |
| Perirectal abscess | 1 ( <0.1) | 6483.90 | 0.02 | 0 | 6495.44 | 0 |
| Pneumonia staphylococcal | 1 ( <0.1) | 6484.36 | 0.02 | 0 | 6495.44 | 0 |
| Pyelonephritis | 1 ( <0.1) | 6484.59 | 0.02 | 0 | 6495.44 | 0 |
| Renal abscess | 1 ( <0.1) | 6484.51 | 0.02 | 0 | 6495.44 | 0 |
| Tooth abscess | 1 ( <0.1) | 6482.75 | 0.02 | 0 | 6495.44 | 0 |
| Cardiac disorders | 33 ( 1.0) | 6475.10 | 0.51 | 24 ( 0.7) | 6490.35 | 0.37 |
| Ischaemic cardiomyopathy | 7 ( 0.2) | 6483.92 | 0.11 | 11 ( 0.3) | 6494.68 | 0.17 |
| Cardiac failure | 10 ( 0.3) | 6483.87 | 0.15 | 7 ( 0.2) | 6495.23 | 0.11 |
| Myocardial infarction | 8 ( 0.2) | 6479.69 | 0.12 | 3 ( 0.1) | 6494.15 | 0.05 |
| Ventricular fibrillation | 0 | 6484.63 | 0 | 2 ( 0.1) | 6494.86 | 0.03 |
| Aortic valve disease | 2 ( 0.1) | 6484.53 | 0.03 | 0 | 6495.44 | 0 |
| Hypertensive cardiomyopathy | 2 ( 0.1) | 6483.32 | 0.03 | 0 | 6495.44 | 0 |
| Aortic valve stenosis | 1 ( <0.1) | 6484.62 | 0.02 | 1 ( <0.1) | 6493.18 | 0.02 |
| Angina pectoris | 1 ( <0.1) | 6483.07 | 0.02 | 0 | 6495.44 | 0 |
| Atrial fibrillation | 1 ( <0.1) | 6484.49 | 0.02 | 0 | 6495.44 | 0 |
| Coronary artery disease | 1 ( <0.1) | 6484.63 | 0.02 | 0 | 6495.44 | 0 |
| General disorders and administration site conditions | 29 ( 0.9) | 6481.77 | 0.45 | 26 ( 0.8) | 6488.47 | 0.40 |
| Sudden cardiac death | 17 ( 0.5) | 6484.62 | 0.26 | 12 ( 0.4) | 6495.44 | 0.18 |
| Death | 9 ( 0.3) | 6484.61 | 0.14 | 10 ( 0.3) | 6495.42 | 0.15 |
| Thirst | 0 | 6484.63 | 0 | 2 ( 0.1) | 6491.38 | 0.03 |
| Oedema peripheral | 2 ( 0.1) | 6481.80 | 0.03 | 1 ( <0.1) | 6493.48 | 0.02 |
| Pain | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.51 | 0.02 |
| Sudden death | 1 ( <0.1) | 6484.63 | 0.02 | 0 | 6495.44 | 0 |

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Table R.1.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the final follow-up visit by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 23 ( 0.7) | 6476.57 | 0.36 | 22 ( 0.7) | 6485.95 | 0.34 |
| Lung cancer metastatic | 3 ( 0.1) | 6484.61 | 0.05 | 0 | 6495.44 | 0 |
| Hepatic cancer | 1 ( <0.1) | 6484.55 | 0.02 | 2 ( 0.1) | 6495.01 | 0.03 |
| Lung neoplasm malignant | 0 | 6484.63 | 0 | 2 ( 0.1) | 6494.08 | 0.03 |
| Pancreatic carcinoma metastatic | 2 ( 0.1) | 6484.47 | 0.03 | 2 ( 0.1) | 6495.43 | 0.03 |
| Pancreatic carcinoma | 2 ( 0.1) | 6484.59 | 0.03 | 0 | 6495.44 | 0 |
| Renal cell carcinoma | 2 ( 0.1) | 6482.56 | 0.03 | 1 ( <0.1) | 6495.44 | 0.02 |
| Adenosquamous cell lung cancer | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.62 | 0.02 |
| Bile duct cancer | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.39 | 0.02 |
| Breast cancer female | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.13 | 0.02 |
| Breast cancer metastatic | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.20 | 0.02 |
| Colon cancer metastatic | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.43 | 0.02 |
| Gallbladder cancer | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.40 | 0.02 |
| Gallbladder cancer metastatic | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.35 | 0.02 |
| Lung adenocarcinoma | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.44 | 0.02 |
| Metastatic bronchial carcinoma | 1 ( <0.1) | 6484.21 | 0.02 | 1 ( <0.1) | 6493.61 | 0.02 |
| Non-small cell lung cancer stage IV | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.16 | 0.02 |
| Ovarian cancer metastatic | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.39 | 0.02 |
| Renal cancer | 0 | 6484.63 | 0 | 1 ( <0.1) | 6493.90 | 0.02 |
| Renal neoplasm | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.16 | 0.02 |
| Small cell lung cancer metastatic | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.44 | 0.02 |
| Squamous cell carcinoma of lung | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.29 | 0.02 |
| Anaplastic astrocytoma | 1 ( <0.1) | 6484.45 | 0.02 | 0 | 6495.44 | 0 |
| Angiosarcoma | 1 ( <0.1) | 6484.53 | 0.02 | 0 | 6495.44 | 0 |
| Colon cancer stage IV | 1 ( <0.1) | 6484.63 | 0.02 | 0 | 6495.44 | 0 |
| Metastatic malignant melanoma | 1 ( <0.1) | 6483.31 | 0.02 | 0 | 6495.44 | 0 |
| Non-Hodgkin's lymphoma | 1 ( <0.1) | 6483.89 | 0.02 | 0 | 6495.44 | 0 |
| Non-small cell lung cancer stage II | 1 ( <0.1) | 6484.61 | 0.02 | 0 | 6495.44 | 0 |
| Oropharyngeal cancer | 1 ( <0.1) | 6484.57 | 0.02 | 0 | 6495.44 | 0 |
| Pancreatic carcinoma stage IV | 1 ( <0.1) | 6484.56 | 0.02 | 0 | 6495.44 | 0 |
| Pleural neoplasm | 1 ( <0.1) | 6484.58 | 0.02 | 0 | 6495.44 | 0 |
| Prostate cancer | 1 ( <0.1) | 6482.71 | 0.02 | 0 | 6495.44 | 0 |
| Rectosigmoid cancer stage II | 1 ( <0.1) | 6483.88 | 0.02 | 0 | 6495.44 | 0 |
| Thymoma malignant | 1 ( <0.1) | 6484.57 | 0.02 | 0 | 6495.44 | 0 |

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Table R.1.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the final follow-up visit by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Renal and urinary disorders | 23 ( 0.7) | 6457.17 | 0.36 | 19 ( 0.6) | 6480.90 | 0.29 |
| End stage renal disease | 12 ( 0.4) | 6474.08 | 0.19 | 9 ( 0.3) | 6490.40 | 0.14 |
| Acute kidney injury | 4 ( 0.1) | 6479.91 | 0.06 | 6 ( 0.2) | 6489.99 | 0.09 |
| Polyuria | 2 ( 0.1) | 6480.39 | 0.03 | 0 | 6495.44 | 0 |
| Diabetic end stage renal disease | 1 ( <0.1) | 6484.01 | 0.02 | 1 ( <0.1) | 6494.96 | 0.02 |
| Glomerulonephritis membranous | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.89 | 0.02 |
| Hydronephrosis | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.65 | 0.02 |
| Nocturia | 0 | 6484.63 | 0 | 1 ( <0.1) | 6493.19 | 0.02 |
| Bladder pain | 1 ( <0.1) | 6482.17 | 0.02 | 0 | 6495.44 | 0 |
| Micturition disorder | 1 ( <0.1) | 6482.30 | 0.02 | 0 | 6495.44 | 0 |
| Renal pain | 1 ( <0.1) | 6482.18 | 0.02 | 0 | 6495.44 | 0 |
| Ureteric obstruction | 1 ( <0.1) | 6484.55 | 0.02 | 0 | 6495.44 | 0 |
| Nervous system disorders | 15 ( 0.5) | 6474.02 | 0.23 | 17 ( 0.5) | 6484.05 | 0.26 |
| Ischaemic stroke | 2 ( 0.1) | 6484.53 | 0.03 | 8 ( 0.2) | 6493.31 | 0.12 |
| Haemorrhagic stroke | 3 ( 0.1) | 6484.61 | 0.05 | 3 ( 0.1) | 6495.29 | 0.05 |
| Burning sensation | 2 ( 0.1) | 6481.49 | 0.03 | 0 | 6495.44 | 0 |
| Cerebral infarction | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.60 | 0.02 |
| Disturbance in attention | 0 | 6484.63 | 0 | 1 ( <0.1) | 6492.80 | 0.02 |
| Dizziness | 1 ( <0.1) | 6483.81 | 0.02 | 1 ( <0.1) | 6493.81 | 0.02 |
| Neuropathy peripheral | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.24 | 0.02 |
| Paraesthesia | 0 | 6484.63 | 0 | 1 ( <0.1) | 6493.98 | 0.02 |
| Sensory disturbance | 0 | 6484.63 | 0 | 1 ( <0.1) | 6493.09 | 0.02 |
| Basilar artery thrombosis | 1 ( <0.1) | 6484.52 | 0.02 | 0 | 6495.44 | 0 |
| Dementia Alzheimer's type | 1 ( <0.1) | 6484.63 | 0.02 | 0 | 6495.44 | 0 |
| Dizziness postural | 1 ( <0.1) | 6482.78 | 0.02 | 0 | 6495.44 | 0 |
| Encephalopathy | 1 ( <0.1) | 6484.57 | 0.02 | 0 | 6495.44 | 0 |
| Headache | 1 ( <0.1) | 6482.39 | 0.02 | 0 | 6495.44 | 0 |
| Lethargy | 1 ( <0.1) | 6482.84 | 0.02 | 0 | 6495.44 | 0 |
| Status epilepticus | 1 ( <0.1) | 6484.15 | 0.02 | 0 | 6495.44 | 0 |

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Table R.1.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the final follow-up visit by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Investigations | 15 ( 0.5) | 6462.32 | 0.23 | 16 ( 0.5) | 6470.76 | 0.25 |
| Blood creatinine increased | 11 ( 0.3) | 6467.98 | 0.17 | 12 ( 0.4) | 6474.08 | 0.19 |
| Blood bilirubin increased | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.42 | 0.02 |
| Blood potassium increased | 1 ( <0.1) | 6483.45 | 0.02 | 1 ( <0.1) | 6494.46 | 0.02 |
| International normalised ratio increased | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.11 | 0.02 |
| Weight decreased | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.44 | 0.02 |
| Blood cholesterol increased | 1 ( <0.1) | 6483.26 | 0.02 | 0 | 6495.44 | 0 |
| Gamma-glutamyltransferase increased | 1 ( <0.1) | 6483.90 | 0.02 | 0 | 6495.44 | 0 |
| Ultrasound abdomen | 1 ( <0.1) | 6482.25 | 0.02 | 0 | 6495.44 | 0 |
| Surgical and medical procedures | 12 ( 0.4) | 6474.07 | 0.19 | 5 ( 0.2) | 6490.23 | 0.08 |
| Dialysis device insertion | 4 ( 0.1) | 6481.47 | 0.06 | 0 | 6495.44 | 0 |
| Arteriovenous shunt operation | 1 ( <0.1) | 6483.40 | 0.02 | 2 ( 0.1) | 6492.98 | 0.03 |
| Gastric operation | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.93 | 0.02 |
| Hospice care | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.35 | 0.02 |
| Toe amputation | 1 ( <0.1) | 6484.33 | 0.02 | 1 ( <0.1) | 6493.29 | 0.02 |
| Arteriovenous fistula operation | 1 ( <0.1) | 6483.67 | 0.02 | 0 | 6495.44 | 0 |
| Coronary artery bypass | 1 ( <0.1) | 6483.59 | 0.02 | 0 | 6495.44 | 0 |
| Gastric bypass | 1 ( <0.1) | 6484.09 | 0.02 | 0 | 6495.44 | 0 |
| Hernia repair | 1 ( <0.1) | 6482.95 | 0.02 | 0 | 6495.44 | 0 |
| Hip surgery | 1 ( <0.1) | 6484.27 | 0.02 | 0 | 6495.44 | 0 |
| Leg amputation | 1 ( <0.1) | 6483.35 | 0.02 | 0 | 6495.44 | 0 |
| Gastrointestinal disorders | 8 ( 0.2) | 6478.17 | 0.12 | 10 ( 0.3) | 6488.56 | 0.15 |
| Constipation | 0 | 6484.63 | 0 | 2 ( 0.1) | 6494.55 | 0.03 |
| Ileus paralytic | 2 ( 0.1) | 6484.53 | 0.03 | 0 | 6495.44 | 0 |
| Gastritis | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.89 | 0.02 |
| Gastrointestinal ischaemia | 1 ( <0.1) | 6484.58 | 0.02 | 1 ( <0.1) | 6495.44 | 0.02 |
| Intestinal obstruction | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.44 | 0.02 |
| Lip swelling | 0 | 6484.63 | 0 | 1 ( <0.1) | 6493.73 | 0.02 |
| Nausea | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.02 | 0.02 |
| Pancreatitis chronic | 0 | 6484.63 | 0 | 1 ( <0.1) | 6493.13 | 0.02 |
| Small intestinal obstruction | 1 ( <0.1) | 6482.69 | 0.02 | 1 ( <0.1) | 6495.43 | 0.02 |
| Upper gastrointestinal haemorrhage | 1 ( <0.1) | 6484.63 | 0.02 | 1 ( <0.1) | 6495.44 | 0.02 |
| Abdominal distension | 1 ( <0.1) | 6484.03 | 0.02 | 0 | 6495.44 | 0 |
| Mouth ulceration | 1 ( <0.1) | 6482.09 | 0.02 | 0 | 6495.44 | 0 |
| Vomiting | 1 ( <0.1) | 6483.39 | 0.02 | 0 | 6495.44 | 0 |

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Table R.1.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the final follow-up visit by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | 4 ( 0.1) | 6475.81 | 0.06 | 7 ( 0.2) | 6485.44 | 0.11 |
| Eczema | 0 | 6484.63 | 0 | 2 ( 0.1) | 6491.26 | 0.03 |
| Pruritus | 1 ( <0.1) | 6482.26 | 0.02 | 2 ( 0.1) | 6492.93 | 0.03 |
| Rash | 2 ( 0.1) | 6480.46 | 0.03 | 1 ( <0.1) | 6493.89 | 0.02 |
| Dermatitis | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.23 | 0.02 |
| Dermatitis atopic | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.89 | 0.02 |
| Rash vesicular | 1 ( <0.1) | 6482.34 | 0.02 | 0 | 6495.44 | 0 |
| Vascular disorders | 7 ( 0.2) | 6479.64 | 0.11 | 7 ( 0.2) | 6490.63 | 0.11 |
| Vasculitis | 0 | 6484.63 | 0 | 2 ( 0.1) | 6492.32 | 0.03 |
| Peripheral vascular disorder | 2 ( 0.1) | 6481.42 | 0.03 | 0 | 6495.44 | 0 |
| Aortic dissection rupture | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.44 | 0.02 |
| Deep vein thrombosis | 1 ( <0.1) | 6484.63 | 0.02 | 1 ( <0.1) | 6495.11 | 0.02 |
| Hypertensive emergency | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.58 | 0.02 |
| Hypovolaemic shock | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.42 | 0.02 |
| Peripheral artery occlusion | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.94 | 0.02 |
| Aortic aneurysm rupture | 1 ( <0.1) | 6484.63 | 0.02 | 0 | 6495.44 | 0 |
| Aortic dissection | 1 ( <0.1) | 6484.63 | 0.02 | 0 | 6495.44 | 0 |
| Aortic occlusion | 1 ( <0.1) | 6484.62 | 0.02 | 0 | 6495.44 | 0 |
| Orthostatic hypotension | 1 ( <0.1) | 6482.85 | 0.02 | 0 | 6495.44 | 0 |
| Hepatobiliary disorders | 4 ( 0.1) | 6481.31 | 0.06 | 6 ( 0.2) | 6492.95 | 0.09 |
| Hepatic cirrhosis | 1 ( <0.1) | 6483.99 | 0.02 | 3 ( 0.1) | 6494.74 | 0.05 |
| Cholangitis | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.29 | 0.02 |
| Hepatitis cholestatic | 0 | 6484.63 | 0 | 1 ( <0.1) | 6493.81 | 0.02 |
| Non-alcoholic fatty liver | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.42 | 0.02 |
| Cholecystitis | 1 ( <0.1) | 6483.93 | 0.02 | 0 | 6495.44 | 0 |
| Hepatic fibrosis | 1 ( <0.1) | 6482.97 | 0.02 | 0 | 6495.44 | 0 |
| Liver injury | 1 ( <0.1) | 6484.31 | 0.02 | 0 | 6495.44 | 0 |
| Metabolism and nutrition disorders | 6 ( 0.2) | 6476.48 | 0.09 | 5 ( 0.2) | 6486.75 | 0.08 |
| Hypoglycaemia | 2 ( 0.1) | 6481.88 | 0.03 | 1 ( <0.1) | 6493.48 | 0.02 |
| Dehydration | 0 | 6484.63 | 0 | 1 ( <0.1) | 6494.44 | 0.02 |
| Gout | 0 | 6484.63 | 0 | 1 ( <0.1) | 6493.13 | 0.02 |
| Hyperglycaemia | 1 ( <0.1) | 6481.94 | 0.02 | 1 ( <0.1) | 6492.96 | 0.02 |
| Hyperkalaemia | 1 ( <0.1) | 6484.58 | 0.02 | 1 ( <0.1) | 6494.49 | 0.02 |
| Diabetes mellitus inadequate control | 1 ( <0.1) | 6482.23 | 0.02 | 0 | 6495.44 | 0 |
| Malnutrition | 1 ( <0.1) | 6484.36 | 0.02 | 0 | 6495.44 | 0 |

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| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Injury, poisoning and procedural complications | 5 ( 0.2) | 6483.27 | 0.08 | 4 ( 0.1) | 6492.68 | 0.06 |
| Burns second degree | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.42 | 0.02 |
| Foreign body aspiration | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.44 | 0.02 |
| Hip fracture | 1 ( <0.1) | 6484.60 | 0.02 | 1 ( <0.1) | 6495.40 | 0.02 |
| Traumatic intracranial haemorrhage | 1 ( <0.1) | 6484.61 | 0.02 | 1 ( <0.1) | 6492.74 | 0.02 |
| Fall | 1 ( <0.1) | 6484.59 | 0.02 | 0 | 6495.44 | 0 |
| Femur fracture | 1 ( <0.1) | 6483.44 | 0.02 | 0 | 6495.44 | 0 |
| Subdural haematoma | 1 ( <0.1) | 6484.55 | 0.02 | 0 | 6495.44 | 0 |
| Respiratory, thoracic and mediastinal disorders | 4 ( 0.1) | 6484.24 | 0.06 | 4 ( 0.1) | 6495.38 | 0.06 |
| Chronic respiratory failure | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.44 | 0.02 |
| Haemothorax | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.38 | 0.02 |
| Pneumothorax | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.44 | 0.02 |
| Respiratory failure | 0 | 6484.63 | 0 | 1 ( <0.1) | 6495.43 | 0.02 |
| Acute respiratory failure | 1 ( <0.1) | 6484.32 | 0.02 | 0 | 6495.44 | 0 |
| Chronic obstructive pulmonary disease | 1 ( <0.1) | 6484.63 | 0.02 | 0 | 6495.44 | 0 |
| Pneumonia aspiration | 1 ( <0.1) | 6484.58 | 0.02 | 0 | 6495.44 | 0 |
| Pulmonary fibrosis | 1 ( <0.1) | 6484.60 | 0.02 | 0 | 6495.44 | 0 |
| Reproductive system and breast disorders | 0 | 6484.63 | 0 | 2 ( 0.1) | 6490.14 | 0.03 |
| Erectile dysfunction | 0 | 6484.63 | 0 | 1 ( <0.1) | 6492.55 | 0.02 |
| Penis disorder | 0 | 6484.63 | 0 | 1 ( <0.1) | 6493.03 | 0.02 |
| Eye disorders | 2 ( 0.1) | 6481.57 | 0.03 | 0 | 6495.44 | 0 |
| Ulcerative keratitis | 1 ( <0.1) | 6482.89 | 0.02 | 0 | 6495.44 | 0 |
| Vitreous haemorrhage | 1 ( <0.1) | 6483.32 | 0.02 | 0 | 6495.44 | 0 |
| Psychiatric disorders | 2 ( 0.1) | 6484.11 | 0.03 | 0 | 6495.44 | 0 |
| Acute psychosis | 1 ( <0.1) | 6484.38 | 0.02 | 0 | 6495.44 | 0 |
| Bipolar disorder | 1 ( <0.1) | 6484.36 | 0.02 | 0 | 6495.44 | 0 |
| Blood and lymphatic system disorders | 1 ( <0.1) | 6484.63 | 0.02 | 0 | 6495.44 | 0 |
| Aplastic anaemia | 1 ( <0.1) | 6484.63 | 0.02 | 0 | 6495.44 | 0 |
| Ear and labyrinth disorders | 1 ( <0.1) | 6482.24 | 0.02 | 0 | 6495.44 | 0 |
| Vertigo positional | 1 ( <0.1) | 6482.24 | 0.02 | 0 | 6495.44 | 0 |

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**R.1.2.3**

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: ^Lower limb amputations (adjudicated)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 19 | 0.6 | 3304 | 28 | 0.8 | 0.1873 | 1.47 ( 0.82, 2.63) | 1.48 ( 0.82, 2.65) | 0.00 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | 0.3066 |
| Male | 2210 | 14 | 0.6 | 2207 | 24 | 1.1 | 0.1024 | 1.72 ( 0.89, 3.31) | 1.72 ( 0.89, 3.34) | 0.00 ( 0.00, 0.01) | |
| Female | 1095 | 5 | 0.5 | 1097 | 4 | 0.4 | 0.7363 | 0.80 ( 0.22, 2.97) | 0.80 ( 0.21, 2.98) | 0.00 (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | 0.4845 |
| <65 | 1501 | 8 | 0.5 | 1501 | 9 | 0.6 | 0.8078 | 1.13 ( 0.44, 2.91) | 1.13 ( 0.43, 2.93) | 0.00 ( 0.00, 0.01) | |
| >=65 | 1804 | 11 | 0.6 | 1803 | 19 | 1.1 | 0.1420 | 1.73 ( 0.82, 3.62) | 1.74 ( 0.82, 3.66) | 0.00 ( 0.00, 0.01) | |
| Region | | | | | | | | | | | 0.2931 |
| North America | 873 | 9 | 1.0 | 844 | 7 | 0.8 | 0.6639 | 0.80 ( 0.30, 2.15) | 0.80 ( 0.30, 2.17) | 0.00 (-0.01, 0.01) | |
| Europe | 1304 | 8 | 0.6 | 1344 | 11 | 0.8 | 0.5322 | 1.33 ( 0.54, 3.31) | 1.34 ( 0.54, 3.33) | 0.00 ( 0.00, 0.01) | |
| Japan | 308 | 0 | 0 | 304 | 2 | 0.7 | 0.2425 | 5.07 ( 0.24,105.08) | 5.10 ( 0.24,106.65) | 0.01 ( 0.00, 0.02) | |
| Other Asia | 820 | 2 | 0.2 | 812 | 8 | 1.0 | 0.0550 | 4.04 ( 0.86, 18.96) | 4.07 ( 0.86, 19.22) | 0.01 ( 0.00, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.4834 |
| Diabetic | 1515 | 17 | 1.1 | 1525 | 23 | 1.5 | 0.3503 | 1.34 ( 0.72, 2.51) | 1.35 ( 0.72, 2.54) | 0.00 ( 0.00, 0.01) | |
| Non-diabetic | 1790 | 2 | 0.1 | 1779 | 5 | 0.3 | 0.2530 | 2.52 ( 0.49, 12.95) | 2.52 ( 0.49, 13.00) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.6689 |
| <30 | 1961 | 9 | 0.5 | 1955 | 15 | 0.8 | 0.2164 | 1.67 ( 0.73, 3.81) | 1.68 ( 0.73, 3.84) | 0.00 ( 0.00, 0.01) | |
| >=30 | 1337 | 10 | 0.7 | 1340 | 13 | 1.0 | 0.5334 | 1.30 ( 0.57, 2.95) | 1.30 ( 0.57, 2.98) | 0.00 ( 0.00, 0.01) | |
| Prior CV disease | | | | | | | | | | | 0.3628 |
| No | 2401 | 6 | 0.2 | 2443 | 13 | 0.5 | 0.1161 | 2.13 ( 0.81, 5.59) | 2.14 ( 0.81, 5.63) | 0.00 ( 0.00, 0.01) | |
| Yes | 904 | 13 | 1.4 | 861 | 15 | 1.7 | 0.6093 | 1.21 ( 0.58, 2.53) | 1.22 ( 0.57, 2.57) | 0.00 (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.4893 |
| <130 | 1208 | 7 | 0.6 | 1190 | 13 | 1.1 | 0.1673 | 1.89 ( 0.75, 4.71) | 1.90 ( 0.75, 4.77) | 0.01 ( 0.00, 0.01) | |
| >=130 | 2097 | 12 | 0.6 | 2114 | 15 | 0.7 | 0.5767 | 1.24 ( 0.58, 2.64) | 1.24 ( 0.58, 2.66) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: ^Lower limb amputations (adjudicated)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.2034 |
| <75 | 1286 | 14 | 1.1 | 1294 | 16 | 1.2 | 0.7262 | 1.14 ( 0.56, 2.32) | 1.14 ( 0.55, 2.34) | 0.00 (-0.01, 0.01) | |
| 75 to <85 | 1033 | 4 | 0.4 | 1019 | 4 | 0.4 | 0.9846 | 1.01 ( 0.25, 4.04) | 1.01 ( 0.25, 4.06) | 0.00 (-0.01, 0.01) | |
| >=85 | 986 | 1 | 0.1 | 991 | 8 | 0.8 | 0.0197 | 7.96 (<1.00, 63.52) | 8.02 ( 1.00, 64.21) | 0.01 ( 0.00, 0.01) | |
| History of heart failure | | | | | | | | | | | 0.3547 |
| No | 2970 | 15 | 0.5 | 2979 | 25 | 0.8 | 0.1148 | 1.66 ( 0.88, 3.15) | 1.67 ( 0.88, 3.17) | 0.00 ( 0.00, 0.01) | |
| Yes | 334 | 4 | 1.2 | 324 | 3 | 0.9 | 0.7342 | 0.77 ( 0.17, 3.43) | 0.77 ( 0.17, 3.47) | 0.00 (-0.02, 0.01) | |
| History of renal disease | | | | | | | | | | | 0.9474 |
| Diabetic kidney disease | 1025 | 13 | 1.3 | 1032 | 21 | 2.0 | 0.1727 | 1.60 ( 0.81, 3.19) | 1.62 ( 0.81, 3.25) | 0.01 ( 0.00, 0.02) | |
| Glomerular disease | 816 | 1 | 0.1 | 853 | 1 | 0.1 | 0.9750 | 0.96 ( 0.06, 15.27) | 0.96 ( 0.06, 15.32) | 0.00 ( 0.00, 0.00) | |
| Hypertensive/renovascular disease | 739 | 2 | 0.3 | 706 | 3 | 0.4 | 0.6176 | 1.57 ( 0.26, 9.37) | 1.57 ( 0.26, 9.44) | 0.00 ( 0.00, 0.01) | |
| Other/Unknown | 725 | 3 | 0.4 | 713 | 3 | 0.4 | 0.9837 | 1.02 ( 0.21, 5.02) | 1.02 ( 0.20, 5.06) | 0.00 (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.4670 |
| <30 | 1151 | 10 | 0.9 | 1131 | 11 | 1.0 | 0.7952 | 1.12 ( 0.48, 2.63) | 1.12 ( 0.47, 2.65) | 0.00 (-0.01, 0.01) | |
| 30 to <45 | 1461 | 6 | 0.4 | 1467 | 14 | 1.0 | 0.0741 | 2.32 ( 0.90, 6.03) | 2.34 ( 0.90, 6.10) | 0.01 ( 0.00, 0.01) | |
| >=45 | 693 | 3 | 0.4 | 706 | 3 | 0.4 | 0.9818 | 0.98 ( 0.20, 4.85) | 0.98 ( 0.20, 4.88) | 0.00 (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.8234 |
| Normal (<30) | 663 | 4 | 0.6 | 665 | 4 | 0.6 | 0.9966 | 1.00 ( 0.25, 3.97) | 1.00 ( 0.25, 4.00) | 0.00 (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 6 | 0.6 | 927 | 10 | 1.1 | 0.3049 | 1.68 ( 0.61, 4.62) | 1.69 ( 0.61, 4.67) | 0.00 ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 9 | 0.5 | 1712 | 14 | 0.8 | 0.3001 | 1.55 ( 0.67, 3.57) | 1.55 ( 0.67, 3.60) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: ^Lower limb amputations (adjudicated)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.8772 |
| Low, moderate or high | 833 | 3 | 0.4 | 839 | 4 | 0.5 | 0.7119 | 1.32 ( 0.30, 5.90) | 1.33 ( 0.30, 5.94) | 0.00 (-0.01, 0.01) | | |
| Very high | 2472 | 16 | 0.6 | 2465 | 24 | 1.0 | 0.2009 | 1.50 ( 0.80, 2.82) | 1.51 ( 0.80, 2.85) | 0.00 ( 0.00, 0.01) | | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | 0.8712 |
| No | 508 | 4 | 0.8 | 473 | 5 | 1.1 | 0.6580 | 1.34 ( 0.36, 4.97) | 1.35 ( 0.36, 5.04) | 0.00 (-0.01, 0.01) | | |
| Yes | 2797 | 15 | 0.5 | 2831 | 23 | 0.8 | 0.2059 | 1.51 ( 0.79, 2.90) | 1.52 ( 0.79, 2.92) | 0.00 ( 0.00, 0.01) | | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3397 |
| No | 1940 | 7 | 0.4 | 1908 | 14 | 0.7 | 0.1164 | 2.03 ( 0.82, 5.03) | 2.04 ( 0.82, 5.07) | 0.00 ( 0.00, 0.01) | | |
| Yes | 1365 | 12 | 0.9 | 1396 | 14 | 1.0 | 0.7364 | 1.14 ( 0.53, 2.46) | 1.14 ( 0.53, 2.48) | 0.00 (-0.01, 0.01) | | |
| Baseline use of diuretics | | | | | | | | | | | | 0.1603 |
| No | 1852 | 8 | 0.4 | 1942 | 7 | 0.4 | 0.7257 | 0.83 ( 0.30, 2.30) | 0.83 ( 0.30, 2.30) | 0.00 ( 0.00, 0.00) | | |
| Yes | 1453 | 11 | 0.8 | 1362 | 21 | 1.5 | 0.0497 | 2.04 ( 0.99, 4.21) | 2.05 ( 0.99, 4.27) | 0.01 ( 0.00, 0.02) | | |

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$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 23 | 0.7 | 3304 | 23 | 0.7 | 0.9992 | 1.00 ( 0.56, 1.78) | 1.00 ( 0.56, 1.79) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | 0.3570 |
| Male | 2210 | 13 | 0.6 | 2207 | 16 | 0.7 | 0.5737 | 1.23 ( 0.59, 2.56) | 1.23 ( 0.59, 2.57) | 0.00 ( 0.00, 0.01) | |
| Female | 1095 | 10 | 0.9 | 1097 | 7 | 0.6 | 0.4628 | 0.70 ( 0.27, 1.83) | 0.70 ( 0.26, 1.84) | 0.00 (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | 0.7632 |
| <65 | 1501 | 10 | 0.7 | 1501 | 9 | 0.6 | 0.8180 | 0.90 ( 0.37, 2.21) | 0.90 ( 0.36, 2.22) | 0.00 (-0.01, 0.01) | |
| >=65 | 1804 | 13 | 0.7 | 1803 | 14 | 0.8 | 0.8457 | 1.08 ( 0.51, 2.29) | 1.08 ( 0.51, 2.30) | 0.00 (-0.01, 0.01) | |
| Region | | | | | | | | | | | 0.4237 |
| North America | 873 | 5 | 0.6 | 844 | 8 | 0.9 | 0.3700 | 1.65 ( 0.54, 5.04) | 1.66 ( 0.54, 5.10) | 0.00 ( 0.00, 0.01) | |
| Europe | 1304 | 11 | 0.8 | 1344 | 7 | 0.5 | 0.3123 | 0.62 ( 0.24, 1.59) | 0.62 ( 0.24, 1.59) | 0.00 (-0.01, 0.00) | |
| Japan | 308 | 1 | 0.3 | 304 | 3 | 1.0 | 0.3094 | 3.04 ( 0.32, 29.06) | 3.06 ( 0.32, 29.58) | 0.01 (-0.01, 0.02) | |
| Other Asia | 820 | 6 | 0.7 | 812 | 5 | 0.6 | 0.7747 | 0.84 ( 0.26, 2.75) | 0.84 ( 0.26, 2.77) | 0.00 (-0.01, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.7753 |
| Diabetic | 1515 | 14 | 0.9 | 1525 | 15 | 1.0 | 0.8660 | 1.06 ( 0.52, 2.20) | 1.07 ( 0.51, 2.21) | 0.00 (-0.01, 0.01) | |
| Non-diabetic | 1790 | 9 | 0.5 | 1779 | 8 | 0.4 | 0.8178 | 0.89 ( 0.35, 2.31) | 0.89 ( 0.34, 2.32) | 0.00 (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.9931 |
| <30 | 1961 | 15 | 0.8 | 1955 | 15 | 0.8 | 0.9933 | 1.00 ( 0.49, 2.05) | 1.00 ( 0.49, 2.06) | 0.00 (-0.01, 0.01) | |
| >=30 | 1337 | 8 | 0.6 | 1340 | 8 | 0.6 | 0.9964 | 1.00 ( 0.38, 2.65) | 1.00 ( 0.37, 2.67) | 0.00 (-0.01, 0.01) | |
| Prior CV disease | | | | | | | | | | | 0.4018 |
| No | 2401 | 14 | 0.6 | 2443 | 17 | 0.7 | 0.6226 | 1.19 ( 0.59, 2.42) | 1.19 ( 0.59, 2.43) | 0.00 ( 0.00, 0.01) | |
| Yes | 904 | 9 | 1.0 | 861 | 6 | 0.7 | 0.4944 | 0.70 ( 0.25, 1.96) | 0.70 ( 0.25, 1.97) | 0.00 (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.1743 |
| <130 | 1208 | 4 | 0.3 | 1190 | 8 | 0.7 | 0.2365 | 2.03 ( 0.61, 6.72) | 2.04 ( 0.61, 6.78) | 0.00 ( 0.00, 0.01) | |
| >=130 | 2097 | 19 | 0.9 | 2114 | 15 | 0.7 | 0.4762 | 0.78 ( 0.40, 1.54) | 0.78 ( 0.40, 1.54) | 0.00 (-0.01, 0.00) | |

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^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.5540 |
| <75 | 1286 | 13 | 1.0 | 1294 | 12 | 0.9 | 0.8286 | 0.92 ( 0.42, 2.00) | 0.92 ( 0.42, 2.02) | 0.00 (-0.01, 0.01) | |
| 75 to <85 | 1033 | 5 | 0.5 | 1019 | 3 | 0.3 | 0.4907 | 0.61 ( 0.15, 2.54) | 0.61 ( 0.14, 2.55) | 0.00 (-0.01, 0.00) | |
| >=85 | 986 | 5 | 0.5 | 991 | 8 | 0.8 | 0.4090 | 1.59 ( 0.52, 4.85) | 1.60 ( 0.52, 4.90) | 0.00 ( 0.00, 0.01) | |
| History of heart failure | | | | | | | | | | | 0.7108 |
| No | 2970 | 19 | 0.6 | 2979 | 20 | 0.7 | 0.8798 | 1.05 ( 0.56, 1.96) | 1.05 ( 0.56, 1.97) | 0.00 ( 0.00, 0.00) | |
| Yes | 334 | 4 | 1.2 | 324 | 3 | 0.9 | 0.7342 | 0.77 ( 0.17, 3.43) | 0.77 ( 0.17, 3.47) | 0.00 (-0.02, 0.01) | |
| History of renal disease | | | | | | | | | | | 0.8158 |
| Diabetic kidney disease | 1025 | 10 | 1.0 | 1032 | 12 | 1.2 | 0.6799 | 1.19 ( 0.52, 2.75) | 1.19 ( 0.51, 2.78) | 0.00 (-0.01, 0.01) | |
| Glomerular disease | 816 | 5 | 0.6 | 853 | 4 | 0.5 | 0.6884 | 0.77 ( 0.21, 2.84) | 0.76 ( 0.20, 2.86) | 0.00 (-0.01, 0.01) | |
| Hypertensive/renovascular disease | 739 | 2 | 0.3 | 706 | 3 | 0.4 | 0.6176 | 1.57 ( 0.26, 9.37) | 1.57 ( 0.26, 9.44) | 0.00 ( 0.00, 0.01) | |
| Other/Unknown | 725 | 6 | 0.8 | 713 | 4 | 0.6 | 0.5431 | 0.68 ( 0.19, 2.39) | 0.68 ( 0.19, 2.41) | 0.00 (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.1460 |
| <30 | 1151 | 12 | 1.0 | 1131 | 7 | 0.6 | 0.2655 | 0.59 ( 0.23, 1.50) | 0.59 ( 0.23, 1.51) | 0.00 (-0.01, 0.00) | |
| 30 to <45 | 1461 | 10 | 0.7 | 1467 | 10 | 0.7 | 0.9927 | 1.00 ( 0.42, 2.39) | 1.00 ( 0.41, 2.40) | 0.00 (-0.01, 0.01) | |
| >=45 | 693 | 1 | 0.1 | 706 | 6 | 0.8 | 0.0615 | 5.89 ( 0.71, 48.79) | 5.93 ( 0.71, 49.40) | 0.01 ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.8975 |
| Normal (<30) | 663 | 4 | 0.6 | 665 | 3 | 0.5 | 0.7017 | 0.75 ( 0.17, 3.33) | 0.75 ( 0.17, 3.35) | 0.00 (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 8 | 0.9 | 927 | 9 | 1.0 | 0.7903 | 1.14 ( 0.44, 2.93) | 1.14 ( 0.44, 2.96) | 0.00 (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 11 | 0.6 | 1712 | 11 | 0.6 | 0.9923 | 1.00 ( 0.43, 2.29) | 1.00 ( 0.43, 2.30) | 0.00 (-0.01, 0.01) | |

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$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0701 |
| Low, moderate or high | 833 | 1 | 0.1 | 839 | 6 | 0.7 | 0.0595 | 5.96 ( 0.72, 49.37) | 5.99 ( 0.72, 49.89) | 0.01 ( 0.00, 0.01) | |
| Very high | 2472 | 22 | 0.9 | 2465 | 17 | 0.7 | 0.4267 | 0.77 ( 0.41, 1.46) | 0.77 ( 0.41, 1.46) | 0.00 (-0.01, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | 0.1166 |
| No | 508 | 8 | 1.6 | 473 | 3 | 0.6 | 0.1621 | 0.40 ( 0.11, 1.51) | 0.40 ( 0.11, 1.51) | -0.01 (-0.02, 0.00) | |
| Yes | 2797 | 15 | 0.5 | 2831 | 20 | 0.7 | 0.4168 | 1.32 ( 0.68, 2.57) | 1.32 ( 0.67, 2.58) | 0.00 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.5081 |
| No | 1940 | 12 | 0.6 | 1908 | 14 | 0.7 | 0.6627 | 1.19 ( 0.55, 2.56) | 1.19 ( 0.55, 2.57) | 0.00 ( 0.00, 0.01) | |
| Yes | 1365 | 11 | 0.8 | 1396 | 9 | 0.6 | 0.6176 | 0.80 ( 0.33, 1.92) | 0.80 ( 0.33, 1.93) | 0.00 (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.6745 |
| No | 1852 | 8 | 0.4 | 1942 | 10 | 0.5 | 0.7101 | 1.19 ( 0.47, 3.01) | 1.19 ( 0.47, 3.03) | 0.00 ( 0.00, 0.01) | |
| Yes | 1453 | 15 | 1.0 | 1362 | 13 | 1.0 | 0.8352 | 0.92 ( 0.44, 1.94) | 0.92 ( 0.44, 1.95) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 1 | <0.1 | 3304 | 6 | 0.2 | 0.0586 | 6.00 ( 0.72, 49.82) | 6.01 ( 0.72, 49.96) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 2210 | 1 | <0.1 | 2207 | 3 | 0.1 | | | | | |
| Female | 1095 | 0 | 0 | 1097 | 3 | 0.3 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 1501 | 0 | 0 | 1501 | 4 | 0.3 | | | | | |
| >=65 | 1804 | 1 | 0.1 | 1803 | 2 | 0.1 | | | | | |
| Region | | | | | | | | | | | |
| North America | 873 | 1 | 0.1 | 844 | 2 | 0.2 | | | | | |
| Europe | 1304 | 0 | 0 | 1344 | 2 | 0.1 | | | | | |
| Japan | 308 | 0 | 0 | 304 | 0 | 0 | | | | | |
| Other Asia | 820 | 0 | 0 | 812 | 2 | 0.2 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 1515 | 1 | 0.1 | 1525 | 5 | 0.3 | | | | | |
| Non-diabetic | 1790 | 0 | 0 | 1779 | 1 | 0.1 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 1961 | 0 | 0 | 1955 | 3 | 0.2 | | | | | |
| >=30 | 1337 | 1 | 0.1 | 1340 | 3 | 0.2 | | | | | |
| Prior CV disease | | | | | | | | | | | |
| No | 2401 | 1 | <0.1 | 2443 | 4 | 0.2 | | | | | |
| Yes | 904 | 0 | 0 | 861 | 2 | 0.2 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 1208 | 0 | 0 | 1190 | 3 | 0.3 | | | | | |
| >=130 | 2097 | 1 | <0.1 | 2114 | 3 | 0.1 | | | | | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 1286 | 1 | 0.1 | 1294 | 4 | 0.3 | | | | | |
| 75 to <85 | 1033 | 0 | 0 | 1019 | 1 | 0.1 | | | | | |
| >=85 | 986 | 0 | 0 | 991 | 1 | 0.1 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 2970 | 1 | <0.1 | 2979 | 4 | 0.1 | | | | | |
| Yes | 334 | 0 | 0 | 324 | 2 | 0.6 | | | | | |
| History of renal disease | | | | | | | | | | | |
| Diabetic kidney disease | 1025 | 1 | 0.1 | 1032 | 5 | 0.5 | | | | | |
| Glomerular disease | 816 | 0 | 0 | 853 | 0 | 0 | | | | | |
| Hypertensive/renovascular disease | 739 | 0 | 0 | 706 | 0 | 0 | | | | | |
| Other/Unknown | 725 | 0 | 0 | 713 | 1 | 0.1 | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 1151 | 0 | 0 | 1131 | 4 | 0.4 | | | | | |
| 30 to <45 | 1461 | 1 | 0.1 | 1467 | 1 | 0.1 | | | | | |
| >=45 | 693 | 0 | 0 | 706 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 663 | 0 | 0 | 665 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 937 | 0 | 0 | 927 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 1705 | 1 | 0.1 | 1712 | 5 | 0.3 | | | | | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 833 | 0 | 0 | 839 | 0 | 0 | | | | | |
| Very high | 2472 | 1 | <0.1 | 2465 | 6 | 0.2 | | | | | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | |
| No | 508 | 0 | 0 | 473 | 0 | 0 | | | | | |
| Yes | 2797 | 1 | <0.1 | 2831 | 6 | 0.2 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 1940 | 0 | 0 | 1908 | 1 | 0.1 | | | | | |
| Yes | 1365 | 1 | 0.1 | 1396 | 5 | 0.4 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 1852 | 0 | 0 | 1942 | 3 | 0.2 | | | | | |
| Yes | 1453 | 1 | 0.1 | 1362 | 3 | 0.2 | | | | | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)$

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 77 | 2.3 | 3304 | 77 | 2.3 | 0.9985 | 1.00 ( 0.73, 1.37) | 1.00 ( 0.73, 1.38) | 0.00 (-0.01, 0.01) | |
| Sex | | | | | | | | | | | 0.7319 |
| Male | 2210 | 45 | 2.0 | 2207 | 47 | 2.1 | 0.8280 | 1.05 ( 0.70, 1.57) | 1.05 ( 0.69, 1.58) | 0.00 (-0.01, 0.01) | |
| Female | 1095 | 32 | 2.9 | 1097 | 30 | 2.7 | 0.7910 | 0.94 ( 0.57, 1.53) | 0.93 ( 0.56, 1.55) | 0.00 (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | 0.2919 |
| <65 | 1501 | 27 | 1.8 | 1501 | 21 | 1.4 | 0.3826 | 0.78 ( 0.44, 1.37) | 0.77 ( 0.44, 1.38) | 0.00 (-0.01, 0.00) | |
| >=65 | 1804 | 50 | 2.8 | 1803 | 56 | 3.1 | 0.5522 | 1.12 ( 0.77, 1.63) | 1.12 ( 0.76, 1.66) | 0.00 (-0.01, 0.01) | |
| Region | | | | | | | | | | | 0.5366 |
| North America | 873 | 37 | 4.2 | 844 | 34 | 4.0 | 0.8272 | 0.95 ( 0.60, 1.50) | 0.95 ( 0.59, 1.53) | 0.00 (-0.02, 0.02) | |
| Europe | 1304 | 28 | 2.1 | 1344 | 24 | 1.8 | 0.5027 | 0.83 ( 0.48, 1.43) | 0.83 ( 0.48, 1.44) | 0.00 (-0.01, 0.01) | |
| Japan | 308 | 6 | 1.9 | 304 | 10 | 3.3 | 0.2984 | 1.69 ( 0.62, 4.59) | 1.71 ( 0.61, 4.77) | 0.01 (-0.01, 0.04) | |
| Other Asia | 820 | 6 | 0.7 | 812 | 9 | 1.1 | 0.4253 | 1.51 ( 0.54, 4.24) | 1.52 ( 0.54, 4.29) | 0.00 (-0.01, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.1310 |
| Diabetic | 1515 | 77 | 5.1 | 1525 | 73 | 4.8 | 0.7067 | 0.94 ( 0.69, 1.29) | 0.94 ( 0.68, 1.30) | 0.00 (-0.02, 0.01) | |
| Non-diabetic | 1790 | 0 | 0 | 1779 | 4 | 0.2 | 0.0723 | 9.06 ( 0.49,168.07) | 9.08 ( 0.49,168.70) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.3434 |
| <30 | 1961 | 28 | 1.4 | 1955 | 34 | 1.7 | 0.4352 | 1.22 ( 0.74, 2.00) | 1.22 ( 0.74, 2.02) | 0.00 ( 0.00, 0.01) | |
| >=30 | 1337 | 48 | 3.6 | 1340 | 43 | 3.2 | 0.5863 | 0.89 ( 0.60, 1.34) | 0.89 ( 0.59, 1.35) | 0.00 (-0.02, 0.01) | |
| Prior CV disease | | | | | | | | | | | 0.4324 |
| No | 2401 | 41 | 1.7 | 2443 | 47 | 1.9 | 0.5731 | 1.13 ( 0.74, 1.71) | 1.13 ( 0.74, 1.72) | 0.00 (-0.01, 0.01) | |
| Yes | 904 | 36 | 4.0 | 861 | 30 | 3.5 | 0.5815 | 0.87 ( 0.54, 1.41) | 0.87 ( 0.53, 1.43) | 0.00 (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.0747 |
| <130 | 1208 | 21 | 1.7 | 1190 | 31 | 2.6 | 0.1452 | 1.50 ( 0.87, 2.59) | 1.51 ( 0.86, 2.65) | 0.01 ( 0.00, 0.02) | |
| >=130 | 2097 | 56 | 2.7 | 2114 | 46 | 2.2 | 0.2966 | 0.81 ( 0.55, 1.20) | 0.81 ( 0.55, 1.20) | 0.00 (-0.01, 0.00) | |

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$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)$

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5552 |
| <75 | 1286 | 47 | 3.7 | 1294 | 44 | 3.4 | 0.7261 | 0.93 ( 0.62, 1.39) | 0.93 ( 0.61, 1.41) | 0.00 | (-0.02, 0.01) | |
| 75 to <85 | 1033 | 20 | 1.9 | 1019 | 18 | 1.8 | 0.7756 | 0.91 ( 0.49, 1.71) | 0.91 ( 0.48, 1.73) | 0.00 | (-0.01, 0.01) | |
| >=85 | 986 | 10 | 1.0 | 991 | 15 | 1.5 | 0.3204 | 1.49 ( 0.67, 3.31) | 1.50 ( 0.67, 3.36) | 0.00 | ( 0.00, 0.01) | |
| History of heart failure | | | | | | | | | | | | 0.4096 |
| No | 2970 | 63 | 2.1 | 2979 | 67 | 2.2 | 0.7359 | 1.06 ( 0.75, 1.49) | 1.06 ( 0.75, 1.50) | 0.00 | (-0.01, 0.01) | |
| Yes | 334 | 14 | 4.2 | 324 | 10 | 3.1 | 0.4496 | 0.74 ( 0.33, 1.63) | 0.73 ( 0.32, 1.66) | -0.01 | (-0.04, 0.02) | |
| History of renal disease | | | | | | | | | | | | 0.3389 |
| Diabetic kidney disease | 1025 | 55 | 5.4 | 1032 | 57 | 5.5 | 0.8750 | 1.03 ( 0.72, 1.48) | 1.03 ( 0.70, 1.51) | 0.00 | (-0.02, 0.02) | |
| Glomerular disease | 816 | 2 | 0.2 | 853 | 5 | 0.6 | 0.2811 | 2.39 ( 0.47, 12.29) | 2.40 ( 0.46, 12.40) | 0.00 | ( 0.00, 0.01) | |
| Hypertensive/renovascular disease | 739 | 10 | 1.4 | 706 | 4 | 0.6 | 0.1270 | 0.42 ( 0.13, 1.33) | 0.42 ( 0.13, 1.33) | -0.01 | (-0.02, 0.00) | |
| Other/Unknown | 725 | 10 | 1.4 | 713 | 11 | 1.5 | 0.7961 | 1.12 ( 0.48, 2.62) | 1.12 ( 0.47, 2.65) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1317 |
| <30 | 1151 | 37 | 3.2 | 1131 | 29 | 2.6 | 0.3539 | 0.80 ( 0.49, 1.29) | 0.79 ( 0.48, 1.30) | -0.01 | (-0.02, 0.01) | |
| 30 to <45 | 1461 | 35 | 2.4 | 1467 | 35 | 2.4 | 0.9862 | 1.00 ( 0.63, 1.58) | 1.00 ( 0.62, 1.60) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 5 | 0.7 | 706 | 13 | 1.8 | 0.0631 | 2.55 ( 0.91, 7.12) | 2.58 ( 0.92, 7.28) | 0.01 | ( 0.00, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8144 |
| Normal (<30) | 663 | 13 | 2.0 | 665 | 14 | 2.1 | 0.8520 | 1.07 ( 0.51, 2.27) | 1.08 ( 0.50, 2.31) | 0.00 | (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 29 | 3.1 | 927 | 25 | 2.7 | 0.6084 | 0.87 ( 0.51, 1.48) | 0.87 ( 0.50, 1.49) | 0.00 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 35 | 2.1 | 1712 | 38 | 2.2 | 0.7359 | 1.08 ( 0.69, 1.70) | 1.08 ( 0.68, 1.72) | 0.00 | (-0.01, 0.01) | |

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Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)$

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3844 |
| Low, moderate or high | 833 | 10 | 1.2 | 839 | 14 | 1.7 | 0.4210 | 1.39 | ( 0.62, 3.11) | 1.40 | ( 0.62, 3.16) | 0.00 | (-0.01, 0.02) | |
| Very high | 2472 | 67 | 2.7 | 2465 | 63 | 2.6 | 0.7345 | 0.94 | ( 0.67, 1.32) | 0.94 | ( 0.66, 1.33) | 0.00 | (-0.01, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.6786 |
| No | 508 | 14 | 2.8 | 473 | 15 | 3.2 | 0.7011 | 1.15 | ( 0.56, 2.36) | 1.16 | ( 0.55, 2.42) | 0.00 | (-0.02, 0.03) | |
| Yes | 2797 | 63 | 2.3 | 2831 | 62 | 2.2 | 0.8739 | 0.97 | ( 0.69, 1.38) | 0.97 | ( 0.68, 1.39) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3919 |
| No | 1940 | 40 | 2.1 | 1908 | 34 | 1.8 | 0.5273 | 0.86 | ( 0.55, 1.36) | 0.86 | ( 0.54, 1.37) | 0.00 | (-0.01, 0.01) | |
| Yes | 1365 | 37 | 2.7 | 1396 | 43 | 3.1 | 0.5627 | 1.14 | ( 0.74, 1.75) | 1.14 | ( 0.73, 1.78) | 0.00 | (-0.01, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.0011 |
| No | 1852 | 14 | 0.8 | 1942 | 35 | 1.8 | 0.0043 | 2.38 | ( 1.29, 4.42) | 2.41 | ( 1.29, 4.49) | 0.01 | ( 0.00, 0.02) | |
| Yes | 1453 | 63 | 4.3 | 1362 | 42 | 3.1 | 0.0798 | 0.71 | ( 0.48, 1.04) | 0.70 | ( 0.47, 1.04) | -0.01 | (-0.03, 0.00) | |

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For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 54 | 1.6 | 3304 | 58 | 1.8 | 0.7019 | 1.07 ( 0.74, 1.55) | 1.08 ( 0.74, 1.56) | 0.00 (-0.01, 0.01) | |
| Sex | | | | | | | | | | | 0.6655 |
| Male | 2210 | 32 | 1.4 | 2207 | 32 | 1.4 | 0.9956 | 1.00 ( 0.62, 1.63) | 1.00 ( 0.61, 1.64) | 0.00 (-0.01, 0.01) | |
| Female | 1095 | 22 | 2.0 | 1097 | 26 | 2.4 | 0.5637 | 1.18 ( 0.67, 2.07) | 1.18 ( 0.67, 2.10) | 0.00 (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | 0.0584 |
| <65 | 1501 | 10 | 0.7 | 1501 | 20 | 1.3 | 0.0665 | 2.00 ( 0.94, 4.26) | 2.01 ( 0.94, 4.32) | 0.01 ( 0.00, 0.01) | |
| >=65 | 1804 | 44 | 2.4 | 1803 | 38 | 2.1 | 0.5043 | 0.86 ( 0.56, 1.33) | 0.86 ( 0.56, 1.34) | 0.00 (-0.01, 0.01) | |
| Region | | | | | | | | | | | 0.5671 |
| North America | 873 | 16 | 1.8 | 844 | 18 | 2.1 | 0.6556 | 1.16 ( 0.60, 2.27) | 1.17 ( 0.59, 2.30) | 0.00 (-0.01, 0.02) | |
| Europe | 1304 | 30 | 2.3 | 1344 | 28 | 2.1 | 0.7025 | 0.91 ( 0.54, 1.51) | 0.90 ( 0.54, 1.52) | 0.00 (-0.01, 0.01) | |
| Japan | 308 | 2 | 0.6 | 304 | 1 | 0.3 | 0.5704 | 0.51 ( 0.05, 5.56) | 0.50 ( 0.05, 5.60) | 0.00 (-0.01, 0.01) | |
| Other Asia | 820 | 6 | 0.7 | 812 | 11 | 1.4 | 0.2152 | 1.85 ( 0.69, 4.98) | 1.86 ( 0.69, 5.06) | 0.01 ( 0.00, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.9325 |
| Diabetic | 1515 | 32 | 2.1 | 1525 | 35 | 2.3 | 0.7313 | 1.09 ( 0.68, 1.75) | 1.09 ( 0.67, 1.77) | 0.00 (-0.01, 0.01) | |
| Non-diabetic | 1790 | 22 | 1.2 | 1779 | 23 | 1.3 | 0.8644 | 1.05 ( 0.59, 1.88) | 1.05 ( 0.58, 1.90) | 0.00 (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.0597 |
| <30 | 1961 | 32 | 1.6 | 1955 | 24 | 1.2 | 0.2868 | 0.75 ( 0.44, 1.27) | 0.75 ( 0.44, 1.28) | 0.00 (-0.01, 0.00) | |
| >=30 | 1337 | 22 | 1.6 | 1340 | 34 | 2.5 | 0.1069 | 1.54 ( 0.91, 2.62) | 1.56 ( 0.91, 2.67) | 0.01 ( 0.00, 0.02) | |
| Prior CV disease | | | | | | | | | | | 0.4323 |
| No | 2401 | 31 | 1.3 | 2443 | 30 | 1.2 | 0.8438 | 0.95 ( 0.58, 1.57) | 0.95 ( 0.57, 1.58) | 0.00 (-0.01, 0.01) | |
| Yes | 904 | 23 | 2.5 | 861 | 28 | 3.3 | 0.3749 | 1.28 ( 0.74, 2.20) | 1.29 ( 0.74, 2.25) | 0.01 (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.1818 |
| <130 | 1208 | 17 | 1.4 | 1190 | 25 | 2.1 | 0.1955 | 1.49 ( 0.81, 2.75) | 1.50 ( 0.81, 2.80) | 0.01 ( 0.00, 0.02) | |
| >=130 | 2097 | 37 | 1.8 | 2114 | 33 | 1.6 | 0.6057 | 0.88 ( 0.56, 1.41) | 0.88 ( 0.55, 1.42) | 0.00 (-0.01, 0.01) | |

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^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9023 |
| <75 | 1286 | 26 | 2.0 | 1294 | 29 | 2.2 | 0.6997 | 1.11 | ( 0.66, 1.87) | 1.11 | ( 0.65, 1.90) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1033 | 15 | 1.5 | 1019 | 17 | 1.7 | 0.6927 | 1.15 | ( 0.58, 2.29) | 1.15 | ( 0.57, 2.32) | 0.00 | (-0.01, 0.01) | |
| >=85 | 986 | 13 | 1.3 | 991 | 12 | 1.2 | 0.8305 | 0.92 | ( 0.42, 2.00) | 0.92 | ( 0.42, 2.02) | 0.00 | (-0.01, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.2854 |
| No | 2970 | 44 | 1.5 | 2979 | 42 | 1.4 | 0.8170 | 0.95 | ( 0.63, 1.45) | 0.95 | ( 0.62, 1.46) | 0.00 | (-0.01, 0.01) | |
| Yes | 334 | 10 | 3.0 | 324 | 15 | 4.6 | 0.2726 | 1.55 | ( 0.70, 3.39) | 1.57 | ( 0.70, 3.55) | 0.02 | (-0.01, 0.05) | |
| History of renal disease | | | | | | | | | | | | | | 0.9741 |
| Diabetic kidney disease | 1025 | 20 | 2.0 | 1032 | 24 | 2.3 | 0.5574 | 1.19 | ( 0.66, 2.14) | 1.20 | ( 0.66, 2.18) | 0.00 | (-0.01, 0.02) | |
| Glomerular disease | 816 | 8 | 1.0 | 853 | 9 | 1.1 | 0.8792 | 1.08 | ( 0.42, 2.78) | 1.08 | ( 0.41, 2.81) | 0.00 | (-0.01, 0.01) | |
| Hypertensive/renovascular disease | 739 | 11 | 1.5 | 706 | 10 | 1.4 | 0.9089 | 0.95 | ( 0.41, 2.23) | 0.95 | ( 0.40, 2.25) | 0.00 | (-0.01, 0.01) | |
| Other/Unknown | 725 | 15 | 2.1 | 713 | 15 | 2.1 | 0.9632 | 1.02 | ( 0.50, 2.06) | 1.02 | ( 0.49, 2.10) | 0.00 | (-0.01, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9783 |
| <30 | 1151 | 19 | 1.7 | 1131 | 21 | 1.9 | 0.7077 | 1.12 | ( 0.61, 2.08) | 1.13 | ( 0.60, 2.11) | 0.00 | (-0.01, 0.01) | |
| 30 to <45 | 1461 | 30 | 2.1 | 1467 | 32 | 2.2 | 0.8100 | 1.06 | ( 0.65, 1.74) | 1.06 | ( 0.64, 1.76) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 5 | 0.7 | 706 | 5 | 0.7 | 0.9765 | 0.98 | ( 0.29, 3.38) | 0.98 | ( 0.28, 3.41) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7832 |
| Normal (<30) | 663 | 12 | 1.8 | 665 | 10 | 1.5 | 0.6620 | 0.83 | ( 0.36, 1.91) | 0.83 | ( 0.36, 1.93) | 0.00 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 21 | 2.2 | 927 | 23 | 2.5 | 0.7330 | 1.11 | ( 0.62, 1.99) | 1.11 | ( 0.61, 2.02) | 0.00 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 1705 | 21 | 1.2 | 1712 | 25 | 1.5 | 0.5621 | 1.19 | ( 0.67, 2.11) | 1.19 | ( 0.66, 2.13) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5704 |
| Low, moderate or high | 833 | 8 | 1.0 | 839 | 11 | 1.3 | 0.4987 | 1.37 ( 0.55, 3.38) | 1.37 ( 0.55, 3.42) | 0.00 | (-0.01, 0.01) | |
| Very high | 2472 | 46 | 1.9 | 2465 | 47 | 1.9 | 0.9057 | 1.02 ( 0.69, 1.53) | 1.03 ( 0.68, 1.55) | 0.00 | (-0.01, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | 0.6664 |
| No | 508 | 12 | 2.4 | 473 | 14 | 3.0 | 0.5604 | 1.25 ( 0.59, 2.68) | 1.26 ( 0.58, 2.75) | 0.01 | (-0.01, 0.03) | |
| Yes | 2797 | 42 | 1.5 | 2831 | 44 | 1.6 | 0.8722 | 1.04 ( 0.68, 1.57) | 1.04 ( 0.68, 1.59) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.0482 |
| No | 1940 | 32 | 1.6 | 1908 | 23 | 1.2 | 0.2459 | 0.73 ( 0.43, 1.24) | 0.73 ( 0.42, 1.25) | 0.00 | (-0.01, 0.00) | |
| Yes | 1365 | 22 | 1.6 | 1396 | 35 | 2.5 | 0.0980 | 1.56 ( 0.92, 2.64) | 1.57 ( 0.92, 2.69) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.8849 |
| No | 1852 | 22 | 1.2 | 1942 | 26 | 1.3 | 0.6776 | 1.13 ( 0.64, 1.98) | 1.13 ( 0.64, 2.00) | 0.00 | (-0.01, 0.01) | |
| Yes | 1453 | 32 | 2.2 | 1362 | 32 | 2.3 | 0.7935 | 1.07 ( 0.66, 1.73) | 1.07 ( 0.65, 1.75) | 0.00 | (-0.01, 0.01) | |

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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 7 | 0.2 | 3304 | 13 | 0.4 | 0.1788 | 1.86 ( 0.74, 4.65) | 1.86 ( 0.74, 4.67) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | 0.1483 |
| Male | 2210 | 7 | 0.3 | 2207 | 8 | 0.4 | 0.7939 | 1.14 ( 0.42, 3.15) | 1.14 ( 0.41, 3.16) | 0.00 ( 0.00, 0.00) | |
| Female | 1095 | 0 | 0 | 1097 | 5 | 0.5 | 0.0412 | 10.98 ( 0.61,198.33) | 11.03 ( 0.61,199.72) | 0.00 ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | 0.1384 |
| <65 | 1501 | 4 | 0.3 | 1501 | 3 | 0.2 | 0.7051 | 0.75 ( 0.17, 3.35) | 0.75 ( 0.17, 3.35) | 0.00 ( 0.00, 0.00) | |
| >=65 | 1804 | 3 | 0.2 | 1803 | 10 | 0.6 | 0.0517 | 3.34 ( 0.92, 12.10) | 3.35 ( 0.92, 12.19) | 0.00 ( 0.00, 0.01) | |
| Region | | | | | | | | | | | 0.4538 |
| North America | 873 | 1 | 0.1 | 844 | 6 | 0.7 | 0.0525 | 6.21 ( 0.75, 51.44) | 6.24 ( 0.75, 51.97) | 0.01 ( 0.00, 0.01) | |
| Europe | 1304 | 5 | 0.4 | 1344 | 7 | 0.5 | 0.5987 | 1.36 ( 0.43, 4.27) | 1.36 ( 0.43, 4.30) | 0.00 ( 0.00, 0.01) | |
| Japan | 308 | 0 | 0 | 304 | 0 | 0 | 0.9948 | 1.01 ( 0.02, 50.89) | 1.01 ( 0.02, 51.22) | 0.00 (-0.01, 0.01) | |
| Other Asia | 820 | 1 | 0.1 | 812 | 0 | 0 | 0.4835 | 0.34 ( 0.01, 8.25) | 0.34 ( 0.01, 8.27) | 0.00 ( 0.00, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.0957 |
| Diabetic | 1515 | 2 | 0.1 | 1525 | 9 | 0.6 | 0.0354 | 4.47 ( 0.97, 20.66) | 4.49 ( 0.97, 20.82) | 0.00 ( 0.00, 0.01) | |
| Non-diabetic | 1790 | 5 | 0.3 | 1779 | 4 | 0.2 | 0.7456 | 0.80 ( 0.22, 2.99) | 0.80 ( 0.22, 3.00) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.5936 |
| <30 | 1961 | 3 | 0.2 | 1955 | 4 | 0.2 | 0.7022 | 1.34 ( 0.30, 5.97) | 1.34 ( 0.30, 5.99) | 0.00 ( 0.00, 0.00) | |
| >=30 | 1337 | 4 | 0.3 | 1340 | 9 | 0.7 | 0.1657 | 2.24 ( 0.69, 7.27) | 2.25 ( 0.69, 7.34) | 0.00 ( 0.00, 0.01) | |
| Prior CV disease | | | | | | | | | | | 0.4878 |
| No | 2401 | 2 | 0.1 | 2443 | 6 | 0.2 | 0.1643 | 2.95 ( 0.60, 14.59) | 2.95 ( 0.60, 14.65) | 0.00 ( 0.00, 0.00) | |
| Yes | 904 | 5 | 0.6 | 861 | 7 | 0.8 | 0.5066 | 1.47 ( 0.47, 4.61) | 1.47 ( 0.47, 4.66) | 0.00 (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.8035 |
| <130 | 1208 | 2 | 0.2 | 1190 | 3 | 0.3 | 0.6423 | 1.52 ( 0.25, 9.10) | 1.52 ( 0.25, 9.14) | 0.00 ( 0.00, 0.00) | |
| >=130 | 2097 | 5 | 0.2 | 2114 | 10 | 0.5 | 0.2014 | 1.98 ( 0.68, 5.79) | 1.99 ( 0.68, 5.83) | 0.00 ( 0.00, 0.01) | |

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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 1286 | 2 | 0.2 | 1294 | 5 | 0.4 | | | | | |
| 75 to <85 | 1033 | 1 | 0.1 | 1019 | 6 | 0.6 | | | | | |
| >=85 | 986 | 4 | 0.4 | 991 | 2 | 0.2 | | | | | |
| History of heart failure | | | | | | | | | | | 0.6226 |
| No | 2970 | 6 | 0.2 | 2979 | 10 | 0.3 | 0.3196 | 1.66 ( 0.60, 4.57) | 1.66 ( 0.60, 4.58) | 0.00 ( 0.00, 0.00) | |
| Yes | 334 | 1 | 0.3 | 324 | 3 | 0.9 | 0.3013 | 3.09 ( 0.32, 29.58) | 3.11 ( 0.32, 30.07) | 0.01 (-0.01, 0.02) | |
| History of renal disease | | | | | | | | | | | |
| Diabetic kidney disease | 1025 | 1 | 0.1 | 1032 | 6 | 0.6 | | | | | |
| Glomerular disease | 816 | 1 | 0.1 | 853 | 1 | 0.1 | | | | | |
| Hypertensive/renovascular disease | 739 | 4 | 0.5 | 706 | 5 | 0.7 | | | | | |
| Other/Unknown | 725 | 1 | 0.1 | 713 | 1 | 0.1 | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 1151 | 2 | 0.2 | 1131 | 7 | 0.6 | | | | | |
| 30 to <45 | 1461 | 2 | 0.1 | 1467 | 4 | 0.3 | | | | | |
| >=45 | 693 | 3 | 0.4 | 706 | 2 | 0.3 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.3865 |
| Normal (<30) | 663 | 1 | 0.2 | 665 | 4 | 0.6 | 0.1800 | 3.99 ( 0.45, 35.59) | 4.01 ( 0.45, 35.94) | 0.00 ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 1 | 0.1 | 927 | 4 | 0.4 | 0.1753 | 4.04 ( 0.45, 36.11) | 4.06 ( 0.45, 36.36) | 0.00 ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 5 | 0.3 | 1712 | 5 | 0.3 | 0.9948 | 1.00 ( 0.29, 3.43) | 1.00 ( 0.29, 3.45) | 0.00 ( 0.00, 0.00) | |

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Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | 0.9261 |
| Low, moderate or high | 833 | 2 | 0.2 | 839 | 4 | 0.5 | 0.4184 | 1.99 ( 0.36, 10.81) | 1.99 ( 0.36, 10.90) | 0.00 ( 0.00, 0.01) | |
| Very high | 2472 | 5 | 0.2 | 2465 | 9 | 0.4 | 0.2820 | 1.81 ( 0.61, 5.38) | 1.81 ( 0.61, 5.40) | 0.00 ( 0.00, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | 0.5951 |
| No | 508 | 1 | 0.2 | 473 | 3 | 0.6 | 0.2827 | 3.22 ( 0.34, 30.87) | 3.24 ( 0.34, 31.22) | 0.00 ( 0.00, 0.01) | |
| Yes | 2797 | 6 | 0.2 | 2831 | 10 | 0.4 | 0.3284 | 1.65 ( 0.60, 4.52) | 1.65 ( 0.60, 4.54) | 0.00 ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.1009 |
| No | 1940 | 5 | 0.3 | 1908 | 4 | 0.2 | 0.7575 | 0.81 ( 0.22, 3.02) | 0.81 ( 0.22, 3.03) | 0.00 ( 0.00, 0.00) | |
| Yes | 1365 | 2 | 0.1 | 1396 | 9 | 0.6 | 0.0377 | 4.40 ( 0.95, 20.33) | 4.42 ( 0.95, 20.50) | 0.00 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.4275 |
| No | 1852 | 2 | 0.1 | 1942 | 2 | 0.1 | 0.9621 | 0.95 ( 0.13, 6.76) | 0.95 ( 0.13, 6.78) | 0.00 ( 0.00, 0.00) | |
| Yes | 1453 | 5 | 0.3 | 1362 | 11 | 0.8 | 0.1021 | 2.35 ( 0.82, 6.74) | 2.36 ( 0.82, 6.80) | 0.00 ( 0.00, 0.01) | |

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Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 10 | 0.3 | 3304 | 13 | 0.4 | 0.5304 | 1.30 ( 0.57, 2.96) | 1.30 ( 0.57, 2.97) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | 0.0569 |
| Male | 2210 | 8 | 0.4 | 2207 | 5 | 0.2 | 0.4061 | 0.63 ( 0.21, 1.91) | 0.63 ( 0.20, 1.91) | 0.00 ( 0.00, 0.00) | |
| Female | 1095 | 2 | 0.2 | 1097 | 8 | 0.7 | 0.0576 | 3.99 ( 0.85, 18.76) | 4.01 ( 0.85, 18.95) | 0.01 ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | 0.6734 |
| <65 | 1501 | 3 | 0.2 | 1501 | 5 | 0.3 | 0.4789 | 1.67 ( 0.40, 6.96) | 1.67 ( 0.40, 7.00) | 0.00 ( 0.00, 0.01) | |
| >=65 | 1804 | 7 | 0.4 | 1803 | 8 | 0.4 | 0.7950 | 1.14 ( 0.42, 3.15) | 1.14 ( 0.41, 3.16) | 0.00 ( 0.00, 0.00) | |
| Region | | | | | | | | | | | 0.2253 |
| North America | 873 | 1 | 0.1 | 844 | 4 | 0.5 | 0.1671 | 4.14 ( 0.46, 36.94) | 4.15 ( 0.46, 37.23) | 0.00 ( 0.00, 0.01) | |
| Europe | 1304 | 7 | 0.5 | 1344 | 6 | 0.4 | 0.7394 | 0.83 ( 0.28, 2.47) | 0.83 ( 0.28, 2.48) | 0.00 (-0.01, 0.00) | |
| Japan | 308 | 2 | 0.6 | 304 | 0 | 0 | 0.2517 | 0.20 (<0.01, 4.20) | 0.20 (<0.01, 4.21) | -0.01 (-0.02, 0.00) | |
| Other Asia | 820 | 0 | 0 | 812 | 3 | 0.4 | 0.1306 | 7.07 ( 0.37,136.63) | 7.10 ( 0.37,137.58) | 0.00 ( 0.00, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.8665 |
| Diabetic | 1515 | 5 | 0.3 | 1525 | 7 | 0.5 | 0.5707 | 1.39 ( 0.44, 4.37) | 1.39 ( 0.44, 4.40) | 0.00 ( 0.00, 0.01) | |
| Non-diabetic | 1790 | 5 | 0.3 | 1779 | 6 | 0.3 | 0.7549 | 1.21 ( 0.37, 3.95) | 1.21 ( 0.37, 3.97) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.8595 |
| <30 | 1961 | 5 | 0.3 | 1955 | 6 | 0.3 | 0.7588 | 1.20 ( 0.37, 3.94) | 1.20 ( 0.37, 3.95) | 0.00 ( 0.00, 0.00) | |
| >=30 | 1337 | 5 | 0.4 | 1340 | 7 | 0.5 | 0.5655 | 1.40 ( 0.44, 4.39) | 1.40 ( 0.44, 4.42) | 0.00 ( 0.00, 0.01) | |
| Prior CV disease | | | | | | | | | | | 0.3127 |
| No | 2401 | 8 | 0.3 | 2443 | 8 | 0.3 | 0.9723 | 0.98 ( 0.37, 2.61) | 0.98 ( 0.37, 2.62) | 0.00 ( 0.00, 0.00) | |
| Yes | 904 | 2 | 0.2 | 861 | 5 | 0.6 | 0.2297 | 2.62 ( 0.51, 13.49) | 2.63 ( 0.51, 13.61) | 0.00 ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.3214 |
| <130 | 1208 | 6 | 0.5 | 1190 | 5 | 0.4 | 0.7816 | 0.85 ( 0.26, 2.76) | 0.85 ( 0.26, 2.78) | 0.00 (-0.01, 0.00) | |
| >=130 | 2097 | 4 | 0.2 | 2114 | 8 | 0.4 | 0.2533 | 1.98 ( 0.60, 6.58) | 1.99 ( 0.60, 6.61) | 0.00 ( 0.00, 0.01) | |

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| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.6784 |
| <75 | 1286 | 4 | 0.3 | 1294 | 7 | 0.5 | 0.3702 | 1.74 ( 0.51, 5.93) | 1.74 ( 0.51, 5.97) | 0.00 ( 0.00, 0.01) | |
| 75 to <85 | 1033 | 2 | 0.2 | 1019 | 3 | 0.3 | 0.6433 | 1.52 ( 0.25, 9.08) | 1.52 ( 0.25, 9.13) | 0.00 ( 0.00, 0.01) | |
| >=85 | 986 | 4 | 0.4 | 991 | 3 | 0.3 | 0.7000 | 0.75 ( 0.17, 3.33) | 0.75 ( 0.17, 3.34) | 0.00 (-0.01, 0.00) | |
| History of heart failure | | | | | | | | | | | 0.2087 |
| No | 2970 | 10 | 0.3 | 2979 | 10 | 0.3 | 0.9946 | 1.00 ( 0.42, 2.39) | 1.00 ( 0.41, 2.40) | 0.00 ( 0.00, 0.00) | |
| Yes | 334 | 0 | 0 | 324 | 3 | 0.9 | 0.1248 | 7.22 ( 0.37,139.14) | 7.28 ( 0.37,141.55) | 0.01 ( 0.00, 0.02) | |
| History of renal disease | | | | | | | | | | | |
| Diabetic kidney disease | 1025 | 3 | 0.3 | 1032 | 4 | 0.4 | | | | | |
| Glomerular disease | 816 | 2 | 0.2 | 853 | 2 | 0.2 | | | | | |
| Hypertensive/renovascular disease | 739 | 1 | 0.1 | 706 | 2 | 0.3 | | | | | |
| Other/Unknown | 725 | 4 | 0.6 | 713 | 5 | 0.7 | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.6274 |
| <30 | 1151 | 2 | 0.2 | 1131 | 5 | 0.4 | 0.2465 | 2.54 ( 0.49, 13.09) | 2.55 ( 0.49, 13.18) | 0.00 ( 0.00, 0.01) | |
| 30 to <45 | 1461 | 7 | 0.5 | 1467 | 7 | 0.5 | 0.9939 | 1.00 ( 0.35, 2.83) | 1.00 ( 0.35, 2.85) | 0.00 (-0.01, 0.00) | |
| >=45 | 693 | 1 | 0.1 | 706 | 1 | 0.1 | 0.9895 | 0.98 ( 0.06, 15.66) | 0.98 ( 0.06, 15.72) | 0.00 ( 0.00, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.8083 |
| Normal (<30) | 663 | 1 | 0.2 | 665 | 2 | 0.3 | 0.5650 | 1.99 ( 0.18, 21.94) | 2.00 ( 0.18, 22.08) | 0.00 ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 6 | 0.6 | 927 | 6 | 0.6 | 0.9851 | 1.01 ( 0.33, 3.12) | 1.01 ( 0.32, 3.15) | 0.00 (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 3 | 0.2 | 1712 | 5 | 0.3 | 0.4826 | 1.66 ( 0.40, 6.93) | 1.66 ( 0.40, 6.96) | 0.00 ( 0.00, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8406 |
| Low, moderate or high | 833 | 1 | 0.1 | 839 | 1 | 0.1 | 0.9959 | 0.99 ( 0.06, 15.85) | 0.99 ( 0.06, 15.90) | 0.00 ( 0.00, 0.00) | |
| Very high | 2472 | 9 | 0.4 | 2465 | 12 | 0.5 | 0.5076 | 1.34 ( 0.56, 3.17) | 1.34 ( 0.56, 3.18) | 0.00 ( 0.00, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | 0.1976 |
| No | 508 | 0 | 0 | 473 | 3 | 0.6 | 0.1152 | 7.52 ( 0.39,145.14) | 7.57 ( 0.39,146.85) | 0.01 ( 0.00, 0.01) | |
| Yes | 2797 | 10 | 0.4 | 2831 | 10 | 0.4 | 0.9784 | 0.99 ( 0.41, 2.37) | 0.99 ( 0.41, 2.38) | 0.00 ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.5406 |
| No | 1940 | 6 | 0.3 | 1908 | 6 | 0.3 | 0.9770 | 1.02 ( 0.33, 3.15) | 1.02 ( 0.33, 3.16) | 0.00 ( 0.00, 0.00) | |
| Yes | 1365 | 4 | 0.3 | 1396 | 7 | 0.5 | 0.3848 | 1.71 ( 0.50, 5.83) | 1.71 ( 0.50, 5.87) | 0.00 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.2507 |
| No | 1852 | 6 | 0.3 | 1942 | 5 | 0.3 | 0.7033 | 0.79 ( 0.24, 2.60) | 0.79 ( 0.24, 2.61) | 0.00 ( 0.00, 0.00) | |
| Yes | 1453 | 4 | 0.3 | 1362 | 8 | 0.6 | 0.2041 | 2.13 ( 0.64, 7.07) | 2.14 ( 0.64, 7.12) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 3305 | 123 | 3.7 | 3304 | 136 | 4.1 | 0.4085 | 1.11 ( 0.87, 1.40) | 1.11 ( 0.87, 1.42) | 0.00 (-0.01, 0.01) | | |
| Sex | | | | | | | | | | | | 0.1969 |
| Male | 2210 | 61 | 2.8 | 2207 | 78 | 3.5 | 0.1407 | 1.28 ( 0.92, 1.78) | 1.29 ( 0.92, 1.81) | 0.01 ( 0.00, 0.02) | | |
| Female | 1095 | 62 | 5.7 | 1097 | 58 | 5.3 | 0.6996 | 0.93 ( 0.66, 1.32) | 0.93 ( 0.64, 1.34) | 0.00 (-0.02, 0.02) | | |
| Age [years] | | | | | | | | | | | | 0.8529 |
| <65 | 1501 | 42 | 2.8 | 1501 | 45 | 3.0 | 0.7441 | 1.07 ( 0.71, 1.62) | 1.07 ( 0.70, 1.65) | 0.00 (-0.01, 0.01) | | |
| >=65 | 1804 | 81 | 4.5 | 1803 | 91 | 5.0 | 0.4324 | 1.12 ( 0.84, 1.51) | 1.13 ( 0.83, 1.54) | 0.01 (-0.01, 0.02) | | |
| Region | | | | | | | | | | | | 0.6110 |
| North America | 873 | 41 | 4.7 | 844 | 34 | 4.0 | 0.4984 | 0.86 ( 0.55, 1.34) | 0.85 ( 0.54, 1.36) | -0.01 (-0.03, 0.01) | | |
| Europe | 1304 | 53 | 4.1 | 1344 | 67 | 5.0 | 0.2548 | 1.23 ( 0.86, 1.74) | 1.24 ( 0.86, 1.79) | 0.01 (-0.01, 0.03) | | |
| Japan | 308 | 14 | 4.5 | 304 | 18 | 5.9 | 0.4447 | 1.30 ( 0.66, 2.57) | 1.32 ( 0.65, 2.71) | 0.01 (-0.02, 0.05) | | |
| Other Asia | 820 | 15 | 1.8 | 812 | 17 | 2.1 | 0.7002 | 1.14 ( 0.58, 2.28) | 1.15 ( 0.57, 2.31) | 0.00 (-0.01, 0.02) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.6803 |
| Diabetic | 1515 | 68 | 4.5 | 1525 | 79 | 5.2 | 0.3739 | 1.15 ( 0.84, 1.58) | 1.16 ( 0.83, 1.62) | 0.01 (-0.01, 0.02) | | |
| Non-diabetic | 1790 | 55 | 3.1 | 1779 | 57 | 3.2 | 0.8219 | 1.04 ( 0.72, 1.50) | 1.04 ( 0.72, 1.52) | 0.00 (-0.01, 0.01) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1221 |
| <30 | 1961 | 75 | 3.8 | 1955 | 70 | 3.6 | 0.6860 | 0.94 ( 0.68, 1.29) | 0.93 ( 0.67, 1.30) | 0.00 (-0.01, 0.01) | | |
| >=30 | 1337 | 48 | 3.6 | 1340 | 66 | 4.9 | 0.0871 | 1.37 ( 0.95, 1.97) | 1.39 ( 0.95, 2.03) | 0.01 ( 0.00, 0.03) | | |
| Prior CV disease | | | | | | | | | | | | 0.2497 |
| No | 2401 | 74 | 3.1 | 2443 | 93 | 3.8 | 0.1669 | 1.24 ( 0.91, 1.67) | 1.24 ( 0.91, 1.70) | 0.01 ( 0.00, 0.02) | | |
| Yes | 904 | 49 | 5.4 | 861 | 43 | 5.0 | 0.6872 | 0.92 ( 0.62, 1.37) | 0.92 ( 0.60, 1.40) | 0.00 (-0.02, 0.02) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7842 |
| <130 | 1208 | 43 | 3.6 | 1190 | 49 | 4.1 | 0.4769 | 1.16 ( 0.77, 1.73) | 1.16 ( 0.77, 1.77) | 0.01 (-0.01, 0.02) | | |
| >=130 | 2097 | 80 | 3.8 | 2114 | 87 | 4.1 | 0.6174 | 1.08 ( 0.80, 1.45) | 1.08 ( 0.79, 1.48) | 0.00 (-0.01, 0.01) | | |

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$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5814 |
| <75 | 1286 | 66 | 5.1 | 1294 | 70 | 5.4 | 0.7526 | 1.05 | ( 0.76, 1.46) | 1.06 | ( 0.75, 1.49) | 0.00 | (-0.01, 0.02) | |
| 75 to <85 | 1033 | 37 | 3.6 | 1019 | 37 | 3.6 | 0.9523 | 1.01 | ( 0.65, 1.59) | 1.01 | ( 0.64, 1.61) | 0.00 | (-0.02, 0.02) | |
| >=85 | 986 | 20 | 2.0 | 991 | 29 | 2.9 | 0.1991 | 1.44 | ( 0.82, 2.53) | 1.46 | ( 0.82, 2.59) | 0.01 | ( 0.00, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.9842 |
| No | 2970 | 108 | 3.6 | 2979 | 120 | 4.0 | 0.4312 | 1.11 | ( 0.86, 1.43) | 1.11 | ( 0.85, 1.45) | 0.00 | (-0.01, 0.01) | |
| Yes | 334 | 15 | 4.5 | 324 | 16 | 4.9 | 0.7866 | 1.10 | ( 0.55, 2.19) | 1.10 | ( 0.54, 2.27) | 0.00 | (-0.03, 0.04) | |
| History of renal disease | | | | | | | | | | | | | | 0.4642 |
| Diabetic kidney disease | 1025 | 45 | 4.4 | 1032 | 48 | 4.7 | 0.7758 | 1.06 | ( 0.71, 1.58) | 1.06 | ( 0.70, 1.61) | 0.00 | (-0.02, 0.02) | |
| Glomerular disease | 816 | 21 | 2.6 | 853 | 25 | 2.9 | 0.6558 | 1.14 | ( 0.64, 2.02) | 1.14 | ( 0.63, 2.06) | 0.00 | (-0.01, 0.02) | |
| Hypertensive/renovascular disease | 739 | 32 | 4.3 | 706 | 26 | 3.7 | 0.5308 | 0.85 | ( 0.51, 1.41) | 0.84 | ( 0.50, 1.43) | -0.01 | (-0.03, 0.01) | |
| Other/Unknown | 725 | 25 | 3.4 | 713 | 37 | 5.2 | 0.1041 | 1.50 | ( 0.92, 2.47) | 1.53 | ( 0.91, 2.57) | 0.02 | ( 0.00, 0.04) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3982 |
| <30 | 1151 | 47 | 4.1 | 1131 | 49 | 4.3 | 0.7670 | 1.06 | ( 0.72, 1.57) | 1.06 | ( 0.71, 1.60) | 0.00 | (-0.01, 0.02) | |
| 30 to <45 | 1461 | 58 | 4.0 | 1467 | 58 | 4.0 | 0.9820 | 1.00 | ( 0.70, 1.42) | 1.00 | ( 0.69, 1.44) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 18 | 2.6 | 706 | 29 | 4.1 | 0.1170 | 1.58 | ( 0.89, 2.82) | 1.61 | ( 0.88, 2.92) | 0.02 | ( 0.00, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1962 |
| Normal (<30) | 663 | 36 | 5.4 | 665 | 30 | 4.5 | 0.4412 | 0.83 | ( 0.52, 1.33) | 0.82 | ( 0.50, 1.35) | -0.01 | (-0.03, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 35 | 3.7 | 927 | 51 | 5.5 | 0.0691 | 1.47 | ( 0.97, 2.24) | 1.50 | ( 0.97, 2.33) | 0.02 | ( 0.00, 0.04) | |
| Macroalbuminuria (>300) | 1705 | 52 | 3.0 | 1712 | 55 | 3.2 | 0.7847 | 1.05 | ( 0.73, 1.53) | 1.06 | ( 0.72, 1.55) | 0.00 | (-0.01, 0.01) | |

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For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5040 |
| Low, moderate or high | 833 | 34 | 4.1 | 839 | 33 | 3.9 | 0.8771 | 0.96 ( 0.60, 1.54) | 0.96 ( 0.59, 1.57) | 0.00 | (-0.02, 0.02) | |
| Very high | 2472 | 89 | 3.6 | 2465 | 103 | 4.2 | 0.2934 | 1.16 ( 0.88, 1.53) | 1.17 ( 0.87, 1.56) | 0.01 | (-0.01, 0.02) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | 0.6676 |
| No | 508 | 18 | 3.5 | 473 | 21 | 4.4 | 0.4727 | 1.25 ( 0.68, 2.32) | 1.26 ( 0.67, 2.40) | 0.01 | (-0.02, 0.03) | |
| Yes | 2797 | 105 | 3.8 | 2831 | 115 | 4.1 | 0.5509 | 1.08 ( 0.83, 1.40) | 1.09 ( 0.83, 1.42) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5902 |
| No | 1940 | 65 | 3.4 | 1908 | 75 | 3.9 | 0.3364 | 1.17 ( 0.85, 1.63) | 1.18 ( 0.84, 1.66) | 0.01 | (-0.01, 0.02) | |
| Yes | 1365 | 58 | 4.2 | 1396 | 61 | 4.4 | 0.8761 | 1.03 ( 0.72, 1.46) | 1.03 ( 0.71, 1.49) | 0.00 | (-0.01, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.0291 |
| No | 1852 | 48 | 2.6 | 1942 | 75 | 3.9 | 0.0272 | 1.49 ( 1.04, 2.13) | 1.51 ( 1.04, 2.18) | 0.01 | ( 0.00, 0.02) | |
| Yes | 1453 | 75 | 5.2 | 1362 | 61 | 4.5 | 0.3983 | 0.87 ( 0.62, 1.21) | 0.86 ( 0.61, 1.22) | -0.01 | (-0.02, 0.01) | |

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For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 15 | 0.5 | 3304 | 18 | 0.5 | 0.6000 | 1.20 ( 0.61, 2.38) | 1.20 ( 0.60, 2.39) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | 0.4810 |
| Male | 2210 | 12 | 0.5 | 2207 | 16 | 0.7 | 0.4461 | 1.34 ( 0.63, 2.82) | 1.34 ( 0.63, 2.83) | 0.00 ( 0.00, 0.01) | |
| Female | 1095 | 3 | 0.3 | 1097 | 2 | 0.2 | 0.6529 | 0.67 ( 0.11, 3.97) | 0.66 ( 0.11, 3.99) | 0.00 ( 0.00, 0.00) | |
| Age [years] | | | | | | | | | | | 0.6048 |
| <65 | 1501 | 3 | 0.2 | 1501 | 5 | 0.3 | 0.4789 | 1.67 ( 0.40, 6.96) | 1.67 ( 0.40, 7.00) | 0.00 ( 0.00, 0.01) | |
| >=65 | 1804 | 12 | 0.7 | 1803 | 13 | 0.7 | 0.8398 | 1.08 ( 0.50, 2.37) | 1.08 ( 0.49, 2.38) | 0.00 ( 0.00, 0.01) | |
| Region | | | | | | | | | | | 0.6619 |
| North America | 873 | 4 | 0.5 | 844 | 7 | 0.8 | 0.3352 | 1.81 ( 0.53, 6.16) | 1.82 ( 0.53, 6.23) | 0.00 ( 0.00, 0.01) | |
| Europe | 1304 | 10 | 0.8 | 1344 | 10 | 0.7 | 0.9459 | 0.97 ( 0.41, 2.32) | 0.97 ( 0.40, 2.34) | 0.00 (-0.01, 0.01) | |
| Japan | 308 | 0 | 0 | 304 | 1 | 0.3 | 0.4731 | 3.04 ( 0.12, 74.32) | 3.05 ( 0.12, 75.15) | 0.00 (-0.01, 0.01) | |
| Other Asia | 820 | 1 | 0.1 | 812 | 0 | 0 | 0.4835 | 0.34 ( 0.01, 8.25) | 0.34 ( 0.01, 8.27) | 0.00 ( 0.00, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.0510 |
| Diabetic | 1515 | 11 | 0.7 | 1525 | 7 | 0.5 | 0.3372 | 0.63 ( 0.25, 1.63) | 0.63 ( 0.24, 1.63) | 0.00 (-0.01, 0.00) | |
| Non-diabetic | 1790 | 4 | 0.2 | 1779 | 11 | 0.6 | 0.0683 | 2.77 ( 0.88, 8.67) | 2.78 ( 0.88, 8.74) | 0.00 ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.7462 |
| <30 | 1961 | 10 | 0.5 | 1955 | 11 | 0.6 | 0.8213 | 1.10 ( 0.47, 2.59) | 1.10 ( 0.47, 2.61) | 0.00 ( 0.00, 0.01) | |
| >=30 | 1337 | 5 | 0.4 | 1340 | 7 | 0.5 | 0.5655 | 1.40 ( 0.44, 4.39) | 1.40 ( 0.44, 4.42) | 0.00 ( 0.00, 0.01) | |
| Prior CV disease | | | | | | | | | | | 0.5146 |
| No | 2401 | 9 | 0.4 | 2443 | 13 | 0.5 | 0.4156 | 1.42 ( 0.61, 3.31) | 1.42 ( 0.61, 3.33) | 0.00 ( 0.00, 0.01) | |
| Yes | 904 | 6 | 0.7 | 861 | 5 | 0.6 | 0.8247 | 0.87 ( 0.27, 2.86) | 0.87 ( 0.27, 2.88) | 0.00 (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.7169 |
| <130 | 1208 | 5 | 0.4 | 1190 | 7 | 0.6 | 0.5453 | 1.42 ( 0.45, 4.47) | 1.42 ( 0.45, 4.50) | 0.00 ( 0.00, 0.01) | |
| >=130 | 2097 | 10 | 0.5 | 2114 | 11 | 0.5 | 0.8413 | 1.09 ( 0.46, 2.56) | 1.09 ( 0.46, 2.58) | 0.00 ( 0.00, 0.00) | |

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$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.7083 |
| <75 | 1286 | 8 | 0.6 | 1294 | 10 | 0.8 | 0.6456 | 1.24 ( 0.49, 3.14) | 1.24 ( 0.49, 3.16) | 0.00 ( 0.00, 0.01) | |
| 75 to <85 | 1033 | 5 | 0.5 | 1019 | 4 | 0.4 | 0.7539 | 0.81 ( 0.22, 3.01) | 0.81 ( 0.22, 3.03) | 0.00 (-0.01, 0.00) | |
| >=85 | 986 | 2 | 0.2 | 991 | 4 | 0.4 | 0.4171 | 1.99 ( 0.37, 10.84) | 1.99 ( 0.36, 10.91) | 0.00 ( 0.00, 0.01) | |
| History of heart failure | | | | | | | | | | | 0.7639 |
| No | 2970 | 13 | 0.4 | 2979 | 15 | 0.5 | 0.7108 | 1.15 ( 0.55, 2.41) | 1.15 ( 0.55, 2.42) | 0.00 ( 0.00, 0.00) | |
| Yes | 334 | 2 | 0.6 | 324 | 3 | 0.9 | 0.6290 | 1.55 ( 0.26, 9.19) | 1.55 ( 0.26, 9.35) | 0.00 (-0.01, 0.02) | |
| History of renal disease | | | | | | | | | | | 0.4073 |
| Diabetic kidney disease | 1025 | 5 | 0.5 | 1032 | 4 | 0.4 | 0.7306 | 0.79 ( 0.21, 2.95) | 0.79 ( 0.21, 2.96) | 0.00 (-0.01, 0.00) | |
| Glomerular disease | 816 | 0 | 0 | 853 | 4 | 0.5 | 0.0814 | 8.61 ( 0.46,159.67) | 8.65 ( 0.47,160.92) | 0.00 ( 0.00, 0.01) | |
| Hypertensive/renovascular disease | 739 | 6 | 0.8 | 706 | 4 | 0.6 | 0.5739 | 0.70 ( 0.20, 2.46) | 0.70 ( 0.20, 2.48) | 0.00 (-0.01, 0.01) | |
| Other/Unknown | 725 | 4 | 0.6 | 713 | 6 | 0.8 | 0.5085 | 1.53 ( 0.43, 5.38) | 1.53 ( 0.43, 5.44) | 0.00 (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.7501 |
| <30 | 1151 | 7 | 0.6 | 1131 | 10 | 0.9 | 0.4433 | 1.45 ( 0.56, 3.81) | 1.46 ( 0.55, 3.84) | 0.00 ( 0.00, 0.01) | |
| 30 to <45 | 1461 | 6 | 0.4 | 1467 | 5 | 0.3 | 0.7574 | 0.83 ( 0.25, 2.71) | 0.83 ( 0.25, 2.72) | 0.00 (-0.01, 0.00) | |
| >=45 | 693 | 2 | 0.3 | 706 | 3 | 0.4 | 0.6692 | 1.47 ( 0.25, 8.78) | 1.47 ( 0.25, 8.85) | 0.00 ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.9267 |
| Normal (<30) | 663 | 4 | 0.6 | 665 | 4 | 0.6 | 0.9966 | 1.00 ( 0.25, 3.97) | 1.00 ( 0.25, 4.00) | 0.00 (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 5 | 0.5 | 927 | 7 | 0.8 | 0.5499 | 1.42 ( 0.45, 4.44) | 1.42 ( 0.45, 4.48) | 0.00 (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 6 | 0.4 | 1712 | 7 | 0.4 | 0.7868 | 1.16 ( 0.39, 3.45) | 1.16 ( 0.39, 3.47) | 0.00 ( 0.00, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.7982 |
| Low, moderate or high | 833 | 2 | 0.2 | 839 | 3 | 0.4 | 0.6600 | 1.49 ( 0.25, | 8.89) | 1.49 ( 0.25, | 8.95) | 0.00 ( 0.00, 0.01) | |
| Very high | 2472 | 13 | 0.5 | 2465 | 15 | 0.6 | 0.6991 | 1.16 ( 0.55, | 2.43) | 1.16 ( 0.55, | 2.44) | 0.00 ( 0.00, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | 0.8768 |
| No | 508 | 3 | 0.6 | 473 | 3 | 0.6 | 0.9301 | 1.07 ( 0.22, | 5.30) | 1.07 ( 0.22, | 5.35) | 0.00 (-0.01, 0.01) | |
| Yes | 2797 | 12 | 0.4 | 2831 | 15 | 0.5 | 0.5842 | 1.23 ( 0.58, | 2.63) | 1.24 ( 0.58, | 2.65) | 0.00 ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.8047 |
| No | 1940 | 7 | 0.4 | 1908 | 9 | 0.5 | 0.5931 | 1.31 ( 0.49, | 3.50) | 1.31 ( 0.49, | 3.52) | 0.00 ( 0.00, 0.01) | |
| Yes | 1365 | 8 | 0.6 | 1396 | 9 | 0.6 | 0.8439 | 1.10 ( 0.43, | 2.84) | 1.10 ( 0.42, | 2.86) | 0.00 (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.1348 |
| No | 1852 | 4 | 0.2 | 1942 | 10 | 0.5 | 0.1290 | 2.38 ( 0.75, | 7.59) | 2.39 ( 0.75, | 7.64) | 0.00 ( 0.00, 0.01) | |
| Yes | 1453 | 11 | 0.8 | 1362 | 8 | 0.6 | 0.5827 | 0.78 ( 0.31, | 1.92) | 0.77 ( 0.31, | 1.93) | 0.00 (-0.01, 0.00) | |

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^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Symptomatic dehydration (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 3305 | 76 | 2.3 | 3304 | 83 | 2.5 | 0.5728 | 1.09 ( 0.80, | 1.49) | 1.09 ( 0.80, | 1.50) | 0.00 (-0.01, | 0.01) | |
| Sex | | | | | | | | | | | | | | 0.7828 |
| Male | 2210 | 47 | 2.1 | 2207 | 53 | 2.4 | 0.5394 | 1.13 ( 0.77, | 1.66) | 1.13 ( 0.76, | 1.68) | 0.00 (-0.01, | 0.01) | |
| Female | 1095 | 29 | 2.6 | 1097 | 30 | 2.7 | 0.9006 | 1.03 ( 0.62, | 1.71) | 1.03 ( 0.62, | 1.73) | 0.00 (-0.01, | 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6780 |
| <65 | 1501 | 26 | 1.7 | 1501 | 31 | 2.1 | 0.5037 | 1.19 ( 0.71, | 2.00) | 1.20 ( 0.71, | 2.02) | 0.00 (-0.01, | 0.01) | |
| >=65 | 1804 | 50 | 2.8 | 1803 | 52 | 2.9 | 0.8386 | 1.04 ( 0.71, | 1.53) | 1.04 ( 0.70, | 1.54) | 0.00 (-0.01, | 0.01) | |
| Region | | | | | | | | | | | | | | 0.5332 |
| North America | 873 | 33 | 3.8 | 844 | 31 | 3.7 | 0.9068 | 0.97 ( 0.60, | 1.57) | 0.97 ( 0.59, | 1.60) | 0.00 (-0.02, | 0.02) | |
| Europe | 1304 | 36 | 2.8 | 1344 | 41 | 3.1 | 0.6572 | 1.10 ( 0.71, | 1.72) | 1.11 ( 0.70, | 1.75) | 0.00 (-0.01, | 0.02) | |
| Japan | 308 | 6 | 1.9 | 304 | 6 | 2.0 | 0.9818 | 1.01 ( 0.33, | 3.11) | 1.01 ( 0.32, | 3.18) | 0.00 (-0.02, | 0.02) | |
| Other Asia | 820 | 1 | 0.1 | 812 | 5 | 0.6 | 0.0993 | 5.05 ( 0.59, | 43.12) | 5.07 ( 0.59, | 43.53) | 0.00 ( 0.00, | 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0388 |
| Diabetic | 1515 | 36 | 2.4 | 1525 | 53 | 3.5 | 0.0723 | 1.46 ( 0.96, | 2.22) | 1.48 ( 0.96, | 2.27) | 0.01 ( 0.00, | 0.02) | |
| Non-diabetic | 1790 | 40 | 2.2 | 1779 | 30 | 1.7 | 0.2376 | 0.75 ( 0.47, | 1.21) | 0.75 ( 0.47, | 1.21) | -0.01 (-0.01, | 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0695 |
| <30 | 1961 | 43 | 2.2 | 1955 | 35 | 1.8 | 0.3674 | 0.82 ( 0.52, | 1.27) | 0.81 ( 0.52, | 1.28) | 0.00 (-0.01, | 0.00) | |
| >=30 | 1337 | 33 | 2.5 | 1340 | 48 | 3.6 | 0.0925 | 1.45 ( 0.94, | 2.25) | 1.47 ( 0.94, | 2.30) | 0.01 ( 0.00, | 0.02) | |
| Prior CV disease | | | | | | | | | | | | | | 0.1163 |
| No | 2401 | 39 | 1.6 | 2443 | 54 | 2.2 | 0.1372 | 1.36 ( 0.90, | 2.05) | 1.37 ( 0.90, | 2.07) | 0.01 ( 0.00, | 0.01) | |
| Yes | 904 | 37 | 4.1 | 861 | 29 | 3.4 | 0.4224 | 0.82 ( 0.51, | 1.33) | 0.82 ( 0.50, | 1.34) | -0.01 (-0.02, | 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9243 |
| <130 | 1208 | 31 | 2.6 | 1190 | 34 | 2.9 | 0.6609 | 1.11 ( 0.69, | 1.80) | 1.12 ( 0.68, | 1.83) | 0.00 (-0.01, | 0.02) | |
| >=130 | 2097 | 45 | 2.1 | 2114 | 49 | 2.3 | 0.7057 | 1.08 ( 0.72, | 1.61) | 1.08 ( 0.72, | 1.63) | 0.00 (-0.01, | 0.01) | |

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Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Symptomatic dehydration (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.9576 |
| <75 | 1286 | 37 | 2.9 | 1294 | 42 | 3.2 | 0.5869 | 1.13 ( 0.73, 1.74) | 1.13 ( 0.72, 1.77) | 0.00 | (-0.01, 0.02) | |
| 75 to <85 | 1033 | 22 | 2.1 | 1019 | 22 | 2.2 | 0.9635 | 1.01 ( 0.56, 1.82) | 1.01 ( 0.56, 1.84) | 0.00 | (-0.01, 0.01) | |
| >=85 | 986 | 17 | 1.7 | 991 | 19 | 1.9 | 0.7481 | 1.11 ( 0.58, 2.13) | 1.11 ( 0.58, 2.16) | 0.00 | (-0.01, 0.01) | |
| History of heart failure | | | | | | | | | | | | 0.2309 |
| No | 2970 | 57 | 1.9 | 2979 | 69 | 2.3 | 0.2876 | 1.21 ( 0.85, 1.71) | 1.21 ( 0.85, 1.73) | 0.00 | ( 0.00, 0.01) | |
| Yes | 334 | 19 | 5.7 | 324 | 14 | 4.3 | 0.4216 | 0.76 ( 0.39, 1.49) | 0.75 ( 0.37, 1.52) | -0.01 | (-0.05, 0.02) | |
| History of renal disease | | | | | | | | | | | | 0.9461 |
| Diabetic kidney disease | 1025 | 26 | 2.5 | 1032 | 30 | 2.9 | 0.6058 | 1.15 ( 0.68, 1.92) | 1.15 ( 0.68, 1.96) | 0.00 | (-0.01, 0.02) | |
| Glomerular disease | 816 | 13 | 1.6 | 853 | 12 | 1.4 | 0.7541 | 0.88 ( 0.41, 1.92) | 0.88 ( 0.40, 1.94) | 0.00 | (-0.01, 0.01) | |
| Hypertensive/renovascular disease | 739 | 17 | 2.3 | 706 | 18 | 2.5 | 0.7581 | 1.11 ( 0.58, 2.13) | 1.11 ( 0.57, 2.17) | 0.00 | (-0.01, 0.02) | |
| Other/Unknown | 725 | 20 | 2.8 | 713 | 23 | 3.2 | 0.6030 | 1.17 ( 0.65, 2.11) | 1.18 ( 0.64, 2.16) | 0.00 | (-0.01, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4078 |
| <30 | 1151 | 31 | 2.7 | 1131 | 42 | 3.7 | 0.1661 | 1.38 ( 0.87, 2.18) | 1.39 ( 0.87, 2.23) | 0.01 | ( 0.00, 0.02) | |
| 30 to <45 | 1461 | 39 | 2.7 | 1467 | 35 | 2.4 | 0.6250 | 0.89 ( 0.57, 1.40) | 0.89 ( 0.56, 1.41) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 6 | 0.9 | 706 | 6 | 0.8 | 0.9742 | 0.98 ( 0.32, 3.03) | 0.98 ( 0.31, 3.06) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4839 |
| Normal (<30) | 663 | 19 | 2.9 | 665 | 23 | 3.5 | 0.5370 | 1.21 ( 0.66, 2.19) | 1.21 ( 0.65, 2.25) | 0.01 | (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 20 | 2.1 | 927 | 27 | 2.9 | 0.2840 | 1.36 ( 0.77, 2.42) | 1.38 ( 0.77, 2.47) | 0.01 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 1705 | 37 | 2.2 | 1712 | 33 | 1.9 | 0.6168 | 0.89 ( 0.56, 1.41) | 0.89 ( 0.55, 1.42) | 0.00 | (-0.01, 0.01) | |

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$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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User-defined AE category: Symptomatic dehydration (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3936 |
| Low, moderate or high | 833 | 14 | 1.7 | 839 | 20 | 2.4 | 0.3084 | 1.42 | ( 0.72, | 2.79) | 1.43 ( 0.72, | 2.85) | 0.01 (-0.01, 0.02) | |
| Very high | 2472 | 62 | 2.5 | 2465 | 63 | 2.6 | 0.9151 | 1.02 | ( 0.72, | 1.44) | 1.02 ( 0.71, | 1.45) | 0.00 (-0.01, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.1245 |
| No | 508 | 17 | 3.3 | 473 | 10 | 2.1 | 0.2385 | 0.63 | ( 0.29, | 1.37) | 0.62 ( 0.28, | 1.38) | -0.01 (-0.03, 0.01) | |
| Yes | 2797 | 59 | 2.1 | 2831 | 73 | 2.6 | 0.2449 | 1.22 | ( 0.87, | 1.72) | 1.23 ( 0.87, | 1.74) | 0.00 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1313 |
| No | 1940 | 39 | 2.0 | 1908 | 32 | 1.7 | 0.4426 | 0.83 | ( 0.52, | 1.33) | 0.83 ( 0.52, | 1.33) | 0.00 (-0.01, 0.01) | |
| Yes | 1365 | 37 | 2.7 | 1396 | 51 | 3.7 | 0.1586 | 1.35 | ( 0.89, | 2.04) | 1.36 ( 0.89, | 2.09) | 0.01 ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3782 |
| No | 1852 | 37 | 2.0 | 1942 | 37 | 1.9 | 0.8367 | 0.95 | ( 0.61, | 1.50) | 0.95 ( 0.60, | 1.51) | 0.00 (-0.01, 0.01) | |
| Yes | 1453 | 39 | 2.7 | 1362 | 46 | 3.4 | 0.2827 | 1.26 | ( 0.83, | 1.92) | 1.27 ( 0.82, | 1.95) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 101 | 3.1 | 3304 | 103 | 3.1 | 0.8852 | 1.02 ( 0.78, | 1.34) | 1.02 ( 0.77, | 1.35) | 0.00 (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | 0.8455 |
| Male | 2210 | 69 | 3.1 | 2207 | 69 | 3.1 | 0.9935 | 1.00 ( 0.72, | 1.39) | 1.00 ( 0.71, | 1.41) | 0.00 (-0.01, 0.01) | |
| Female | 1095 | 32 | 2.9 | 1097 | 34 | 3.1 | 0.8084 | 1.06 ( 0.66, | 1.71) | 1.06 ( 0.65, | 1.73) | 0.00 (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | | | 0.2611 |
| <65 | 1501 | 28 | 1.9 | 1501 | 36 | 2.4 | 0.3121 | 1.29 ( 0.79, | 2.10) | 1.29 ( 0.78, | 2.13) | 0.01 (-0.01, 0.02) | |
| >=65 | 1804 | 73 | 4.0 | 1803 | 67 | 3.7 | 0.6073 | 0.92 ( 0.66, | 1.27) | 0.92 ( 0.65, | 1.28) | 0.00 (-0.02, 0.01) | |
| Region | | | | | | | | | | | | | 0.9680 |
| North America | 873 | 40 | 4.6 | 844 | 37 | 4.4 | 0.8429 | 0.96 ( 0.62, | 1.48) | 0.95 ( 0.60, | 1.51) | 0.00 (-0.02, 0.02) | |
| Europe | 1304 | 51 | 3.9 | 1344 | 54 | 4.0 | 0.8880 | 1.03 ( 0.71, | 1.49) | 1.03 ( 0.70, | 1.52) | 0.00 (-0.01, 0.02) | |
| Japan | 308 | 6 | 1.9 | 304 | 7 | 2.3 | 0.7610 | 1.18 ( 0.40, | 3.48) | 1.19 ( 0.39, | 3.57) | 0.00 (-0.02, 0.03) | |
| Other Asia | 820 | 4 | 0.5 | 812 | 5 | 0.6 | 0.7271 | 1.26 ( 0.34, | 4.68) | 1.26 ( 0.34, | 4.72) | 0.00 (-0.01, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.0525 |
| Diabetic | 1515 | 51 | 3.4 | 1525 | 66 | 4.3 | 0.1682 | 1.29 ( 0.90, | 1.84) | 1.30 ( 0.89, | 1.88) | 0.01 ( 0.00, 0.02) | |
| Non-diabetic | 1790 | 50 | 2.8 | 1779 | 37 | 2.1 | 0.1670 | 0.74 ( 0.49, | 1.13) | 0.74 ( 0.48, | 1.14) | -0.01 (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.0076 |
| <30 | 1961 | 61 | 3.1 | 1955 | 43 | 2.2 | 0.0762 | 0.71 ( 0.48, | 1.04) | 0.70 ( 0.47, | 1.04) | -0.01 (-0.02, 0.00) | |
| >=30 | 1337 | 40 | 3.0 | 1340 | 60 | 4.5 | 0.0427 | 1.50 ( 1.01, | 2.22) | 1.52 ( 1.01, | 2.28) | 0.01 ( 0.00, 0.03) | |
| Prior CV disease | | | | | | | | | | | | | 0.2379 |
| No | 2401 | 50 | 2.1 | 2443 | 61 | 2.5 | 0.3351 | 1.20 ( 0.83, | 1.74) | 1.20 ( 0.82, | 1.76) | 0.00 ( 0.00, 0.01) | |
| Yes | 904 | 51 | 5.6 | 861 | 42 | 4.9 | 0.4730 | 0.86 ( 0.58, | 1.29) | 0.86 ( 0.56, | 1.30) | -0.01 (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.9741 |
| <130 | 1208 | 40 | 3.3 | 1190 | 40 | 3.4 | 0.9456 | 1.02 ( 0.66, | 1.56) | 1.02 ( 0.65, | 1.59) | 0.00 (-0.01, 0.01) | |
| >=130 | 2097 | 61 | 2.9 | 2114 | 63 | 3.0 | 0.8913 | 1.02 ( 0.72, | 1.45) | 1.03 ( 0.72, | 1.47) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8576 |
| <75 | 1286 | 50 | 3.9 | 1294 | 55 | 4.3 | 0.6414 | 1.09 | ( 0.75, 1.59) | 1.10 | ( 0.74, 1.62) | 0.00 | (-0.01, 0.02) | |
| 75 to <85 | 1033 | 28 | 2.7 | 1019 | 27 | 2.6 | 0.9319 | 0.98 | ( 0.58, 1.65) | 0.98 | ( 0.57, 1.67) | 0.00 | (-0.01, 0.01) | |
| >=85 | 986 | 23 | 2.3 | 991 | 21 | 2.1 | 0.7475 | 0.91 | ( 0.51, 1.63) | 0.91 | ( 0.50, 1.65) | 0.00 | (-0.02, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.7411 |
| No | 2970 | 79 | 2.7 | 2979 | 83 | 2.8 | 0.7649 | 1.05 | ( 0.77, 1.42) | 1.05 | ( 0.77, 1.43) | 0.00 | (-0.01, 0.01) | |
| Yes | 334 | 22 | 6.6 | 324 | 20 | 6.2 | 0.8281 | 0.94 | ( 0.52, 1.68) | 0.93 | ( 0.50, 1.74) | 0.00 | (-0.04, 0.03) | |
| History of renal disease | | | | | | | | | | | | | | 0.6838 |
| Diabetic kidney disease | 1025 | 36 | 3.5 | 1032 | 38 | 3.7 | 0.8360 | 1.05 | ( 0.67, 1.64) | 1.05 | ( 0.66, 1.67) | 0.00 | (-0.01, 0.02) | |
| Glomerular disease | 816 | 18 | 2.2 | 853 | 13 | 1.5 | 0.3024 | 0.69 | ( 0.34, 1.40) | 0.69 | ( 0.33, 1.41) | -0.01 | (-0.02, 0.01) | |
| Hypertensive/renovascular disease | 739 | 21 | 2.8 | 706 | 23 | 3.3 | 0.6454 | 1.15 | ( 0.64, 2.05) | 1.15 | ( 0.63, 2.10) | 0.00 | (-0.01, 0.02) | |
| Other/Unknown | 725 | 26 | 3.6 | 713 | 29 | 4.1 | 0.6344 | 1.13 | ( 0.67, 1.91) | 1.14 | ( 0.66, 1.96) | 0.00 | (-0.02, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7966 |
| <30 | 1151 | 45 | 3.9 | 1131 | 50 | 4.4 | 0.5410 | 1.13 | ( 0.76, 1.68) | 1.14 | ( 0.75, 1.72) | 0.01 | (-0.01, 0.02) | |
| 30 to <45 | 1461 | 48 | 3.3 | 1467 | 45 | 3.1 | 0.7367 | 0.93 | ( 0.63, 1.39) | 0.93 | ( 0.62, 1.41) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 8 | 1.2 | 706 | 8 | 1.1 | 0.9702 | 0.98 | ( 0.37, 2.60) | 0.98 | ( 0.37, 2.63) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1969 |
| Normal (<30) | 663 | 22 | 3.3 | 665 | 31 | 4.7 | 0.2111 | 1.40 | ( 0.82, 2.40) | 1.42 | ( 0.82, 2.49) | 0.01 | (-0.01, 0.03) | |
| Microalbuminuria (30 to <=300) | 937 | 28 | 3.0 | 927 | 32 | 3.5 | 0.5706 | 1.16 | ( 0.70, 1.90) | 1.16 | ( 0.69, 1.94) | 0.00 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 1705 | 51 | 3.0 | 1712 | 40 | 2.3 | 0.2346 | 0.78 | ( 0.52, 1.18) | 0.78 | ( 0.51, 1.18) | -0.01 | (-0.02, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.1072 |
| Low, moderate or high | 833 | 17 | 2.0 | 839 | 27 | 3.2 | 0.1327 | 1.58 ( 0.87, 2.87) | 1.60 ( 0.86, 2.95) | 0.01 ( 0.00, 0.03) | | |
| Very high | 2472 | 84 | 3.4 | 2465 | 76 | 3.1 | 0.5321 | 0.91 ( 0.67, 1.23) | 0.90 ( 0.66, 1.24) | 0.00 (-0.01, 0.01) | | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | 0.1459 |
| No | 508 | 24 | 4.7 | 473 | 15 | 3.2 | 0.2135 | 0.67 ( 0.36, 1.26) | 0.66 ( 0.34, 1.27) | -0.02 (-0.04, 0.01) | | |
| Yes | 2797 | 77 | 2.8 | 2831 | 88 | 3.1 | 0.4293 | 1.13 ( 0.84, 1.53) | 1.13 ( 0.83, 1.55) | 0.00 (-0.01, 0.01) | | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.1569 |
| No | 1940 | 50 | 2.6 | 1908 | 40 | 2.1 | 0.3237 | 0.81 ( 0.54, 1.23) | 0.81 ( 0.53, 1.23) | 0.00 (-0.01, 0.00) | | |
| Yes | 1365 | 51 | 3.7 | 1396 | 63 | 4.5 | 0.3051 | 1.21 ( 0.84, 1.73) | 1.22 ( 0.84, 1.78) | 0.01 (-0.01, 0.02) | | |
| Baseline use of diuretics | | | | | | | | | | | | 0.4174 |
| No | 1852 | 44 | 2.4 | 1942 | 42 | 2.2 | 0.6594 | 0.91 ( 0.60, 1.38) | 0.91 ( 0.59, 1.39) | 0.00 (-0.01, 0.01) | | |
| Yes | 1453 | 57 | 3.9 | 1362 | 61 | 4.5 | 0.4621 | 1.14 ( 0.80, 1.63) | 1.15 ( 0.79, 1.66) | 0.01 (-0.01, 0.02) | | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 30 | 0.9 | 3304 | 24 | 0.7 | 0.4129 | 0.80 ( 0.47, 1.37) | 0.80 ( 0.47, 1.37) | 0.00 (-0.01, 0.00) | |
| Sex | | | | | | | | | | | 0.4539 |
| Male | 2210 | 25 | 1.1 | 2207 | 18 | 0.8 | 0.2854 | 0.72 ( 0.39, 1.32) | 0.72 ( 0.39, 1.32) | 0.00 (-0.01, 0.00) | |
| Female | 1095 | 5 | 0.5 | 1097 | 6 | 0.5 | 0.7648 | 1.20 ( 0.37, 3.91) | 1.20 ( 0.36, 3.94) | 0.00 (-0.01, 0.01) | |
| Age [years] | | | | | | | | | | | 0.2785 |
| <65 | 1501 | 4 | 0.3 | 1501 | 6 | 0.4 | 0.5264 | 1.50 ( 0.42, 5.30) | 1.50 ( 0.42, 5.33) | 0.00 ( 0.00, 0.01) | |
| >=65 | 1804 | 26 | 1.4 | 1803 | 18 | 1.0 | 0.2257 | 0.69 ( 0.38, 1.26) | 0.69 ( 0.38, 1.26) | 0.00 (-0.01, 0.00) | |
| Region | | | | | | | | | | | 0.4219 |
| North America | 873 | 12 | 1.4 | 844 | 7 | 0.8 | 0.2803 | 0.60 ( 0.24, 1.53) | 0.60 ( 0.24, 1.53) | -0.01 (-0.02, 0.00) | |
| Europe | 1304 | 15 | 1.2 | 1344 | 16 | 1.2 | 0.9235 | 1.03 ( 0.51, 2.08) | 1.04 ( 0.51, 2.10) | 0.00 (-0.01, 0.01) | |
| Japan | 308 | 0 | 0 | 304 | 1 | 0.3 | 0.4731 | 3.04 ( 0.12, 74.32) | 3.05 ( 0.12, 75.15) | 0.00 (-0.01, 0.01) | |
| Other Asia | 820 | 3 | 0.4 | 812 | 0 | 0 | 0.1357 | 0.14 (<0.01, 2.79) | 0.14 (<0.01, 2.79) | 0.00 (-0.01, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.8688 |
| Diabetic | 1515 | 18 | 1.2 | 1525 | 15 | 1.0 | 0.5864 | 0.83 ( 0.42, 1.64) | 0.83 ( 0.41, 1.65) | 0.00 (-0.01, 0.01) | |
| Non-diabetic | 1790 | 12 | 0.7 | 1779 | 9 | 0.5 | 0.5206 | 0.75 ( 0.32, 1.79) | 0.75 ( 0.32, 1.79) | 0.00 (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.0624 |
| <30 | 1961 | 19 | 1.0 | 1955 | 9 | 0.5 | 0.0590 | 0.48 ( 0.22, 1.05) | 0.47 ( 0.21, 1.05) | -0.01 (-0.01, 0.00) | |
| >=30 | 1337 | 11 | 0.8 | 1340 | 15 | 1.1 | 0.4339 | 1.36 ( 0.63, 2.95) | 1.36 ( 0.62, 2.98) | 0.00 ( 0.00, 0.01) | |
| Prior CV disease | | | | | | | | | | | 0.5796 |
| No | 2401 | 13 | 0.5 | 2443 | 9 | 0.4 | 0.3705 | 0.68 ( 0.29, 1.59) | 0.68 ( 0.29, 1.59) | 0.00 (-0.01, 0.00) | |
| Yes | 904 | 17 | 1.9 | 861 | 15 | 1.7 | 0.8276 | 0.93 ( 0.47, 1.84) | 0.93 ( 0.46, 1.86) | 0.00 (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.9170 |
| <130 | 1208 | 11 | 0.9 | 1190 | 9 | 0.8 | 0.6779 | 0.83 ( 0.35, 2.00) | 0.83 ( 0.34, 2.01) | 0.00 (-0.01, 0.01) | |
| >=130 | 2097 | 19 | 0.9 | 2114 | 15 | 0.7 | 0.4762 | 0.78 ( 0.40, 1.54) | 0.78 ( 0.40, 1.54) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5952 |
| <75 | 1286 | 16 | 1.2 | 1294 | 15 | 1.2 | 0.8430 | 0.93 ( 0.46, | 1.88) | 0.93 ( 0.46, | 1.89) | 0.00 (-0.01, | 0.01) | |
| 75 to <85 | 1033 | 7 | 0.7 | 1019 | 6 | 0.6 | 0.7998 | 0.87 ( 0.29, | 2.58) | 0.87 ( 0.29, | 2.59) | 0.00 (-0.01, | 0.01) | |
| >=85 | 986 | 7 | 0.7 | 991 | 3 | 0.3 | 0.2019 | 0.43 ( 0.11, | 1.64) | 0.42 ( 0.11, | 1.65) | 0.00 (-0.01, | 0.00) | |
| History of heart failure | | | | | | | | | | | | | | 0.1432 |
| No | 2970 | 25 | 0.8 | 2979 | 16 | 0.5 | 0.1556 | 0.64 ( 0.34, | 1.19) | 0.64 ( 0.34, | 1.19) | 0.00 (-0.01, | 0.00) | |
| Yes | 334 | 5 | 1.5 | 324 | 8 | 2.5 | 0.3703 | 1.65 ( 0.55, | 4.99) | 1.67 ( 0.54, | 5.15) | 0.01 (-0.01, | 0.03) | |
| History of renal disease | | | | | | | | | | | | | | 0.3943 |
| Diabetic kidney disease | 1025 | 13 | 1.3 | 1032 | 9 | 0.9 | 0.3824 | 0.69 ( 0.30, | 1.60) | 0.68 ( 0.29, | 1.61) | 0.00 (-0.01, | 0.00) | |
| Glomerular disease | 816 | 5 | 0.6 | 853 | 1 | 0.1 | 0.0909 | 0.19 ( 0.02, | 1.63) | 0.19 ( 0.02, | 1.63) | 0.00 (-0.01, | 0.00) | |
| Hypertensive/renovascular disease | 739 | 6 | 0.8 | 706 | 6 | 0.8 | 0.9367 | 1.05 ( 0.34, | 3.23) | 1.05 ( 0.34, | 3.26) | 0.00 (-0.01, | 0.01) | |
| Other/Unknown | 725 | 6 | 0.8 | 713 | 8 | 1.1 | 0.5697 | 1.36 ( 0.47, | 3.89) | 1.36 ( 0.47, | 3.94) | 0.00 (-0.01, | 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8778 |
| <30 | 1151 | 16 | 1.4 | 1131 | 11 | 1.0 | 0.3564 | 0.70 ( 0.33, | 1.50) | 0.70 ( 0.32, | 1.51) | 0.00 (-0.01, | 0.00) | |
| 30 to <45 | 1461 | 12 | 0.8 | 1467 | 11 | 0.7 | 0.8265 | 0.91 ( 0.40, | 2.06) | 0.91 ( 0.40, | 2.07) | 0.00 (-0.01, | 0.01) | |
| >=45 | 693 | 2 | 0.3 | 706 | 2 | 0.3 | 0.9852 | 0.98 ( 0.14, | 6.95) | 0.98 ( 0.14, | 6.99) | 0.00 (-0.01, | 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1203 |
| Normal (<30) | 663 | 4 | 0.6 | 665 | 9 | 1.4 | 0.1651 | 2.24 ( 0.69, | 7.25) | 2.26 ( 0.69, | 7.38) | 0.01 ( 0.00, | 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 10 | 1.1 | 927 | 7 | 0.8 | 0.4785 | 0.71 ( 0.27, | 1.85) | 0.71 ( 0.27, | 1.86) | 0.00 (-0.01, | 0.01) | |
| Macroalbuminuria (>300) | 1705 | 16 | 0.9 | 1712 | 8 | 0.5 | 0.0992 | 0.50 ( 0.21, | 1.16) | 0.50 ( 0.21, | 1.16) | 0.00 (-0.01, | 0.00) | |

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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0892 |
| Low, moderate or high | 833 | 4 | 0.5 | 839 | 8 | 1.0 | 0.2516 | 1.99 ( 0.60, 6.57) | 2.00 ( 0.60, 6.65) | 0.00 ( 0.00, 0.01) | | |
| Very high | 2472 | 26 | 1.1 | 2465 | 16 | 0.6 | 0.1235 | 0.62 ( 0.33, 1.15) | 0.61 ( 0.33, 1.15) | 0.00 (-0.01, 0.00) | | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | 0.7107 |
| No | 508 | 8 | 1.6 | 473 | 5 | 1.1 | 0.4786 | 0.67 ( 0.22, 2.04) | 0.67 ( 0.22, 2.06) | -0.01 (-0.02, 0.01) | | |
| Yes | 2797 | 22 | 0.8 | 2831 | 19 | 0.7 | 0.6107 | 0.85 ( 0.46, 1.57) | 0.85 ( 0.46, 1.58) | 0.00 (-0.01, 0.00) | | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9059 |
| No | 1940 | 12 | 0.6 | 1908 | 9 | 0.5 | 0.5364 | 0.76 ( 0.32, 1.81) | 0.76 ( 0.32, 1.81) | 0.00 (-0.01, 0.00) | | |
| Yes | 1365 | 18 | 1.3 | 1396 | 15 | 1.1 | 0.5550 | 0.81 ( 0.41, 1.61) | 0.81 ( 0.41, 1.62) | 0.00 (-0.01, 0.01) | | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9840 |
| No | 1852 | 8 | 0.4 | 1942 | 7 | 0.4 | 0.7257 | 0.83 ( 0.30, 2.30) | 0.83 ( 0.30, 2.30) | 0.00 ( 0.00, 0.00) | | |
| Yes | 1453 | 22 | 1.5 | 1362 | 17 | 1.2 | 0.5463 | 0.82 ( 0.44, 1.55) | 0.82 ( 0.43, 1.55) | 0.00 (-0.01, 0.01) | | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 135 | 4.1 | 3304 | 107 | 3.2 | 0.0670 | 0.79 ( 0.62, | 1.02) | 0.79 ( 0.61, | 1.02) | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | 0.1874 |
| Male | 2210 | 100 | 4.5 | 2207 | 71 | 3.2 | 0.0243 | 0.71 ( 0.53, | 0.96) | 0.70 ( 0.51, | 0.96) | -0.01 (-0.02, 0.00) | |
| Female | 1095 | 35 | 3.2 | 1097 | 36 | 3.3 | 0.9102 | 1.03 ( 0.65, | 1.62) | 1.03 ( 0.64, | 1.65) | 0.00 (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | | | 0.9100 |
| <65 | 1501 | 47 | 3.1 | 1501 | 38 | 2.5 | 0.3220 | 0.81 ( 0.53, | 1.23) | 0.80 ( 0.52, | 1.24) | -0.01 (-0.02, 0.01) | |
| >=65 | 1804 | 88 | 4.9 | 1803 | 69 | 3.8 | 0.1219 | 0.78 ( 0.58, | 1.07) | 0.78 ( 0.56, | 1.07) | -0.01 (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | 0.7577 |
| North America | 873 | 45 | 5.2 | 844 | 37 | 4.4 | 0.4540 | 0.85 ( 0.56, | 1.30) | 0.84 ( 0.54, | 1.32) | -0.01 (-0.03, 0.01) | |
| Europe | 1304 | 58 | 4.4 | 1344 | 48 | 3.6 | 0.2501 | 0.80 ( 0.55, | 1.17) | 0.80 ( 0.54, | 1.18) | -0.01 (-0.02, 0.01) | |
| Japan | 308 | 4 | 1.3 | 304 | 1 | 0.3 | 0.1827 | 0.25 ( 0.03, | 2.25) | 0.25 ( 0.03, | 2.26) | -0.01 (-0.02, 0.00) | |
| Other Asia | 820 | 28 | 3.4 | 812 | 21 | 2.6 | 0.3268 | 0.76 ( 0.43, | 1.32) | 0.75 ( 0.42, | 1.33) | -0.01 (-0.02, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.1959 |
| Diabetic | 1515 | 81 | 5.3 | 1525 | 73 | 4.8 | 0.4817 | 0.90 ( 0.66, | 1.22) | 0.89 ( 0.64, | 1.23) | -0.01 (-0.02, 0.01) | |
| Non-diabetic | 1790 | 54 | 3.0 | 1779 | 34 | 1.9 | 0.0332 | 0.63 ( 0.41, | 0.97) | 0.63 ( 0.41, | 0.97) | -0.01 (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.1246 |
| <30 | 1961 | 65 | 3.3 | 1955 | 41 | 2.1 | 0.0189 | 0.63 ( 0.43, | 0.93) | 0.62 ( 0.42, | 0.93) | -0.01 (-0.02, 0.00) | |
| >=30 | 1337 | 70 | 5.2 | 1340 | 66 | 4.9 | 0.7148 | 0.94 ( 0.68, | 1.31) | 0.94 ( 0.66, | 1.32) | 0.00 (-0.02, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | 0.6573 |
| No | 2401 | 76 | 3.2 | 2443 | 59 | 2.4 | 0.1127 | 0.76 ( 0.55, | 1.07) | 0.76 ( 0.54, | 1.07) | -0.01 (-0.02, 0.00) | |
| Yes | 904 | 59 | 6.5 | 861 | 48 | 5.6 | 0.4024 | 0.85 ( 0.59, | 1.24) | 0.85 ( 0.57, | 1.25) | -0.01 (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.1446 |
| <130 | 1208 | 37 | 3.1 | 1190 | 38 | 3.2 | 0.8545 | 1.04 ( 0.67, | 1.63) | 1.04 ( 0.66, | 1.65) | 0.00 (-0.01, 0.02) | |
| >=130 | 2097 | 98 | 4.7 | 2114 | 69 | 3.3 | 0.0191 | 0.70 ( 0.52, | 0.94) | 0.69 ( 0.50, | 0.94) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.4726 |
| <75 | 1286 | 61 | 4.7 | 1294 | 55 | 4.3 | 0.5457 | 0.90 ( 0.63, 1.28) | 0.89 ( 0.61, 1.29) | 0.00 (-0.02, 0.01) | |
| 75 to <85 | 1033 | 44 | 4.3 | 1019 | 27 | 2.6 | 0.0461 | 0.62 ( 0.39, <1.00) | 0.61 ( 0.38, 1.00) | -0.02 (-0.03, 0.00) | |
| >=85 | 986 | 30 | 3.0 | 991 | 25 | 2.5 | 0.4822 | 0.83 ( 0.49, 1.40) | 0.82 ( 0.48, 1.41) | -0.01 (-0.02, 0.01) | |
| History of heart failure | | | | | | | | | | | 0.0272 |
| No | 2970 | 113 | 3.8 | 2979 | 78 | 2.6 | 0.0094 | 0.69 ( 0.52, 0.91) | 0.68 ( 0.51, 0.91) | -0.01 (-0.02, 0.00) | |
| Yes | 334 | 22 | 6.6 | 324 | 29 | 9.0 | 0.2569 | 1.36 ( 0.80, 2.31) | 1.39 ( 0.78, 2.48) | 0.02 (-0.02, 0.06) | |
| History of renal disease | | | | | | | | | | | 0.3683 |
| Diabetic kidney disease | 1025 | 61 | 6.0 | 1032 | 49 | 4.7 | 0.2252 | 0.80 ( 0.55, 1.15) | 0.79 ( 0.54, 1.16) | -0.01 (-0.03, 0.01) | |
| Glomerular disease | 816 | 20 | 2.5 | 853 | 12 | 1.4 | 0.1200 | 0.57 ( 0.28, 1.17) | 0.57 ( 0.28, 1.17) | -0.01 (-0.02, 0.00) | |
| Hypertensive/renovascular disease | 739 | 28 | 3.8 | 706 | 17 | 2.4 | 0.1309 | 0.64 ( 0.35, 1.15) | 0.63 ( 0.34, 1.16) | -0.01 (-0.03, 0.00) | |
| Other/Unknown | 725 | 26 | 3.6 | 713 | 29 | 4.1 | 0.6344 | 1.13 ( 0.67, 1.91) | 1.14 ( 0.66, 1.96) | 0.00 (-0.02, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.2078 |
| <30 | 1151 | 63 | 5.5 | 1131 | 60 | 5.3 | 0.8586 | 0.97 ( 0.69, 1.37) | 0.97 ( 0.67, 1.39) | 0.00 (-0.02, 0.02) | |
| 30 to <45 | 1461 | 57 | 3.9 | 1467 | 40 | 2.7 | 0.0757 | 0.70 ( 0.47, 1.04) | 0.69 ( 0.46, 1.04) | -0.01 (-0.02, 0.00) | |
| >=45 | 693 | 15 | 2.2 | 706 | 7 | 1.0 | 0.0779 | 0.46 ( 0.19, 1.12) | 0.45 ( 0.18, 1.12) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.4615 |
| Normal (<30) | 663 | 17 | 2.6 | 665 | 17 | 2.6 | 0.9929 | 1.00 ( 0.51, 1.94) | 1.00 ( 0.50, 1.97) | 0.00 (-0.02, 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 41 | 4.4 | 927 | 37 | 4.0 | 0.6787 | 0.91 ( 0.59, 1.41) | 0.91 ( 0.58, 1.43) | 0.00 (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 77 | 4.5 | 1712 | 53 | 3.1 | 0.0300 | 0.69 ( 0.49, 0.97) | 0.68 ( 0.47, 0.96) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4092 |
| Low, moderate or high | 833 | 17 | 2.0 | 839 | 10 | 1.2 | 0.1685 | 0.58 ( 0.27, 1.27) | 0.58 ( 0.26, 1.27) | -0.01 | (-0.02, 0.00) | |
| Very high | 2472 | 118 | 4.8 | 2465 | 97 | 3.9 | 0.1490 | 0.82 ( 0.63, 1.07) | 0.82 ( 0.62, 1.08) | -0.01 | (-0.02, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | 0.4285 |
| No | 508 | 27 | 5.3 | 473 | 16 | 3.4 | 0.1396 | 0.64 ( 0.35, 1.17) | 0.62 ( 0.33, 1.17) | -0.02 | (-0.04, 0.01) | |
| Yes | 2797 | 108 | 3.9 | 2831 | 91 | 3.2 | 0.1889 | 0.83 ( 0.63, 1.09) | 0.83 ( 0.62, 1.10) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4782 |
| No | 1940 | 59 | 3.0 | 1908 | 41 | 2.1 | 0.0819 | 0.71 ( 0.48, 1.05) | 0.70 ( 0.47, 1.05) | -0.01 | (-0.02, 0.00) | |
| Yes | 1365 | 76 | 5.6 | 1396 | 66 | 4.7 | 0.3178 | 0.85 ( 0.62, 1.17) | 0.84 ( 0.60, 1.18) | -0.01 | (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.4572 |
| No | 1852 | 47 | 2.5 | 1942 | 45 | 2.3 | 0.6588 | 0.91 ( 0.61, 1.37) | 0.91 ( 0.60, 1.38) | 0.00 | (-0.01, 0.01) | |
| Yes | 1453 | 88 | 6.1 | 1362 | 62 | 4.6 | 0.0758 | 0.75 ( 0.55, 1.03) | 0.74 ( 0.53, 1.03) | -0.02 | (-0.03, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 317 | 9.6 | 3304 | 278 | 8.4 | 0.0945 | 0.88 ( 0.75, | 1.02) | 0.87 ( 0.73, | 1.03) | -0.01 (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | 0.0241 |
| Male | 2210 | 229 | 10.4 | 2207 | 222 | 10.1 | 0.7394 | 0.97 ( 0.81, | 1.16) | 0.97 ( 0.80, | 1.18) | 0.00 (-0.02, 0.01) | |
| Female | 1095 | 88 | 8.0 | 1097 | 56 | 5.1 | 0.0056 | 0.64 ( 0.46, | 0.88) | 0.62 ( 0.44, | 0.87) | -0.03 (-0.05,-0.01) | |
| Age [years] | | | | | | | | | | | | | 0.0278 |
| <65 | 1501 | 163 | 10.9 | 1501 | 119 | 7.9 | 0.0059 | 0.73 ( 0.58, | 0.91) | 0.71 ( 0.55, | 0.91) | -0.03 (-0.05,-0.01) | |
| >=65 | 1804 | 154 | 8.5 | 1803 | 159 | 8.8 | 0.7635 | 1.03 ( 0.84, | 1.28) | 1.04 ( 0.82, | 1.31) | 0.00 (-0.02, 0.02) | |
| Region | | | | | | | | | | | | | 0.2228 |
| North America | 873 | 90 | 10.3 | 844 | 63 | 7.5 | 0.0386 | 0.72 ( 0.53, | 0.98) | 0.70 ( 0.50, | 0.98) | -0.03 (-0.06, 0.00) | |
| Europe | 1304 | 151 | 11.6 | 1344 | 157 | 11.7 | 0.9349 | 1.01 ( 0.82, | 1.24) | 1.01 ( 0.80, | 1.28) | 0.00 (-0.02, 0.03) | |
| Japan | 308 | 3 | 1.0 | 304 | 4 | 1.3 | 0.6910 | 1.35 ( 0.30, | 5.99) | 1.36 ( 0.30, | 6.11) | 0.00 (-0.01, 0.02) | |
| Other Asia | 820 | 73 | 8.9 | 812 | 54 | 6.7 | 0.0895 | 0.75 ( 0.53, | 1.05) | 0.73 ( 0.51, | 1.05) | -0.02 (-0.05, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.1392 |
| Diabetic | 1515 | 129 | 8.5 | 1525 | 130 | 8.5 | 0.9923 | 1.00 ( 0.79, | 1.26) | 1.00 ( 0.78, | 1.29) | 0.00 (-0.02, 0.02) | |
| Non-diabetic | 1790 | 188 | 10.5 | 1779 | 148 | 8.3 | 0.0255 | 0.79 ( 0.65, | 0.97) | 0.77 ( 0.62, | 0.97) | -0.02 (-0.04, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.4408 |
| <30 | 1961 | 160 | 8.2 | 1955 | 132 | 6.8 | 0.0937 | 0.83 ( 0.66, | 1.03) | 0.82 ( 0.64, | 1.04) | -0.01 (-0.03, 0.00) | |
| >=30 | 1337 | 156 | 11.7 | 1340 | 146 | 10.9 | 0.5276 | 0.93 ( 0.75, | 1.16) | 0.93 ( 0.73, | 1.18) | -0.01 (-0.03, 0.02) | |
| Prior CV disease | | | | | | | | | | | | | 0.0437 |
| No | 2401 | 235 | 9.8 | 2443 | 190 | 7.8 | 0.0134 | 0.79 ( 0.66, | 0.95) | 0.78 ( 0.64, | 0.95) | -0.02 (-0.04, 0.00) | |
| Yes | 904 | 82 | 9.1 | 861 | 88 | 10.2 | 0.4131 | 1.13 ( 0.85, | 1.50) | 1.14 ( 0.83, | 1.57) | 0.01 (-0.02, 0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.0042 |
| <130 | 1208 | 133 | 11.0 | 1190 | 85 | 7.1 | 0.0010 | 0.65 ( 0.50, | 0.84) | 0.62 ( 0.47, | 0.83) | -0.04 (-0.06,-0.02) | |
| >=130 | 2097 | 184 | 8.8 | 2114 | 193 | 9.1 | 0.6865 | 1.04 ( 0.86, | 1.26) | 1.04 ( 0.85, | 1.29) | 0.00 (-0.01, 0.02) | |

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$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
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For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.8174 |
| <75 | 1286 | 116 | 9.0 | 1294 | 105 | 8.1 | 0.4111 | 0.90 ( 0.70, 1.16) | 0.89 ( 0.68, 1.17) | -0.01 | (-0.03, 0.01) | |
| 75 to <85 | 1033 | 109 | 10.6 | 1019 | 88 | 8.6 | 0.1408 | 0.82 ( 0.63, 1.07) | 0.80 ( 0.60, 1.08) | -0.02 | (-0.04, 0.01) | |
| >=85 | 986 | 92 | 9.3 | 991 | 85 | 8.6 | 0.5574 | 0.92 ( 0.69, 1.22) | 0.91 ( 0.67, 1.24) | -0.01 | (-0.03, 0.02) | |
| History of heart failure | | | | | | | | | | | | 0.3147 |
| No | 2970 | 285 | 9.6 | 2979 | 244 | 8.2 | 0.0569 | 0.85 ( 0.73, >1.00) | 0.84 ( 0.70, 1.01) | -0.01 | (-0.03, 0.00) | |
| Yes | 334 | 32 | 9.6 | 324 | 34 | 10.5 | 0.6967 | 1.10 ( 0.69, 1.73) | 1.11 ( 0.67, 1.84) | 0.01 | (-0.04, 0.06) | |
| History of renal disease | | | | | | | | | | | | 0.4040 |
| Diabetic kidney disease | 1025 | 80 | 7.8 | 1032 | 86 | 8.3 | 0.6600 | 1.07 ( 0.80, 1.43) | 1.07 ( 0.78, 1.48) | 0.01 | (-0.02, 0.03) | |
| Glomerular disease | 816 | 73 | 8.9 | 853 | 63 | 7.4 | 0.2441 | 0.83 ( 0.60, 1.14) | 0.81 ( 0.57, 1.15) | -0.02 | (-0.04, 0.01) | |
| Hypertensive/renovascular disease | 739 | 77 | 10.4 | 706 | 65 | 9.2 | 0.4389 | 0.88 ( 0.65, 1.21) | 0.87 ( 0.62, 1.23) | -0.01 | (-0.04, 0.02) | |
| Other/Unknown | 725 | 87 | 12.0 | 713 | 64 | 9.0 | 0.0615 | 0.75 ( 0.55, 1.02) | 0.72 ( 0.51, 1.02) | -0.03 | (-0.06, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.9339 |
| <30 | 1151 | 127 | 11.0 | 1131 | 107 | 9.5 | 0.2155 | 0.86 ( 0.67, 1.09) | 0.84 ( 0.64, 1.11) | -0.02 | (-0.04, 0.01) | |
| 30 to <45 | 1461 | 145 | 9.9 | 1467 | 132 | 9.0 | 0.3916 | 0.91 ( 0.72, 1.13) | 0.90 ( 0.70, 1.15) | -0.01 | (-0.03, 0.01) | |
| >=45 | 693 | 45 | 6.5 | 706 | 39 | 5.5 | 0.4454 | 0.85 ( 0.56, 1.29) | 0.84 ( 0.54, 1.31) | -0.01 | (-0.03, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.1944 |
| Normal (<30) | 663 | 82 | 12.4 | 665 | 56 | 8.4 | 0.0184 | 0.68 ( 0.49, 0.94) | 0.65 ( 0.46, 0.93) | -0.04 | (-0.07,-0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 91 | 9.7 | 927 | 81 | 8.7 | 0.4675 | 0.90 ( 0.68, 1.20) | 0.89 ( 0.65, 1.22) | -0.01 | (-0.04, 0.02) | |
| Macroalbuminuria (>300) | 1705 | 144 | 8.4 | 1712 | 141 | 8.2 | 0.8245 | 0.98 ( 0.78, 1.22) | 0.97 ( 0.76, 1.24) | 0.00 | (-0.02, 0.02) | |

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$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0900 |
| Low, moderate or high | 833 | 75 | 9.0 | 839 | 51 | 6.1 | 0.0235 | 0.68 ( 0.48, 0.95) | 0.65 ( 0.45, 0.95) | -0.03 | (-0.05, 0.00) | |
| Very high | 2472 | 242 | 9.8 | 2465 | 227 | 9.2 | 0.4866 | 0.94 ( 0.79, 1.12) | 0.93 ( 0.77, 1.13) | -0.01 | (-0.02, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | 0.7460 |
| No | 508 | 32 | 6.3 | 473 | 24 | 5.1 | 0.4085 | 0.81 ( 0.48, 1.35) | 0.80 ( 0.46, 1.37) | -0.01 | (-0.04, 0.02) | |
| Yes | 2797 | 285 | 10.2 | 2831 | 254 | 9.0 | 0.1207 | 0.88 ( 0.75, 1.03) | 0.87 ( 0.73, 1.04) | -0.01 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.8528 |
| No | 1940 | 173 | 8.9 | 1908 | 147 | 7.7 | 0.1730 | 0.86 ( 0.70, 1.07) | 0.85 ( 0.68, 1.07) | -0.01 | (-0.03, 0.01) | |
| Yes | 1365 | 144 | 10.5 | 1396 | 131 | 9.4 | 0.3066 | 0.89 ( 0.71, 1.11) | 0.88 ( 0.68, 1.13) | -0.01 | (-0.03, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.8572 |
| No | 1852 | 136 | 7.3 | 1942 | 125 | 6.4 | 0.2700 | 0.88 ( 0.69, 1.11) | 0.87 ( 0.67, 1.12) | -0.01 | (-0.03, 0.01) | |
| Yes | 1453 | 181 | 12.5 | 1362 | 153 | 11.2 | 0.3158 | 0.90 ( 0.74, 1.10) | 0.89 ( 0.71, 1.12) | -0.01 | (-0.04, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 3305 | 109 | 3.3 | 3304 | 92 | 2.8 | 0.2241 | 0.84 ( 0.64, | 1.11) | 0.84 ( 0.63, | 1.11) | -0.01 (-0.01, | 0.00) | |
| Sex | | | | | | | | | | | | | | 0.5944 |
| Male | 2210 | 77 | 3.5 | 2207 | 68 | 3.1 | 0.4522 | 0.88 ( 0.64, | 1.22) | 0.88 ( 0.63, | 1.23) | 0.00 (-0.01, | 0.01) | |
| Female | 1095 | 32 | 2.9 | 1097 | 24 | 2.2 | 0.2758 | 0.75 ( 0.44, | 1.26) | 0.74 ( 0.43, | 1.27) | -0.01 (-0.02, | 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.2881 |
| <65 | 1501 | 47 | 3.1 | 1501 | 33 | 2.2 | 0.1126 | 0.70 ( 0.45, | 1.09) | 0.70 ( 0.44, | 1.09) | -0.01 (-0.02, | 0.00) | |
| >=65 | 1804 | 62 | 3.4 | 1803 | 59 | 3.3 | 0.7838 | 0.95 ( 0.67, | 1.35) | 0.95 ( 0.66, | 1.37) | 0.00 (-0.01, | 0.01) | |
| Region | | | | | | | | | | | | | | 0.9462 |
| North America | 873 | 35 | 4.0 | 844 | 27 | 3.2 | 0.3684 | 0.80 ( 0.49, | 1.31) | 0.79 ( 0.47, | 1.32) | -0.01 (-0.03, | 0.01) | |
| Europe | 1304 | 54 | 4.1 | 1344 | 50 | 3.7 | 0.5773 | 0.90 ( 0.62, | 1.31) | 0.89 ( 0.60, | 1.32) | 0.00 (-0.02, | 0.01) | |
| Japan | 308 | 2 | 0.6 | 304 | 1 | 0.3 | 0.5704 | 0.51 ( 0.05, | 5.56) | 0.50 ( 0.05, | 5.60) | 0.00 (-0.01, | 0.01) | |
| Other Asia | 820 | 18 | 2.2 | 812 | 14 | 1.7 | 0.4926 | 0.79 ( 0.39, | 1.57) | 0.78 ( 0.39, | 1.58) | 0.00 (-0.02, | 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5704 |
| Diabetic | 1515 | 62 | 4.1 | 1525 | 49 | 3.2 | 0.1962 | 0.79 ( 0.54, | 1.13) | 0.78 ( 0.53, | 1.14) | -0.01 (-0.02, | 0.00) | |
| Non-diabetic | 1790 | 47 | 2.6 | 1779 | 43 | 2.4 | 0.6910 | 0.92 ( 0.61, | 1.38) | 0.92 ( 0.60, | 1.40) | 0.00 (-0.01, | 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3597 |
| <30 | 1961 | 56 | 2.9 | 1955 | 53 | 2.7 | 0.7832 | 0.95 ( 0.66, | 1.37) | 0.95 ( 0.65, | 1.39) | 0.00 (-0.01, | 0.01) | |
| >=30 | 1337 | 53 | 4.0 | 1340 | 39 | 2.9 | 0.1346 | 0.73 ( 0.49, | 1.10) | 0.73 ( 0.48, | 1.11) | -0.01 (-0.02, | 0.00) | |
| Prior CV disease | | | | | | | | | | | | | | 0.9188 |
| No | 2401 | 76 | 3.2 | 2443 | 66 | 2.7 | 0.3387 | 0.85 ( 0.62, | 1.18) | 0.85 ( 0.61, | 1.19) | 0.00 (-0.01, | 0.00) | |
| Yes | 904 | 33 | 3.7 | 861 | 26 | 3.0 | 0.4612 | 0.83 ( 0.50, | 1.37) | 0.82 ( 0.49, | 1.39) | -0.01 (-0.02, | 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7343 |
| <130 | 1208 | 29 | 2.4 | 1190 | 26 | 2.2 | 0.7241 | 0.91 ( 0.54, | 1.54) | 0.91 ( 0.53, | 1.55) | 0.00 (-0.01, | 0.01) | |
| >=130 | 2097 | 80 | 3.8 | 2114 | 66 | 3.1 | 0.2191 | 0.82 ( 0.59, | 1.13) | 0.81 ( 0.58, | 1.13) | -0.01 (-0.02, | 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.0428 |
| <75 | 1286 | 44 | 3.4 | 1294 | 42 | 3.2 | 0.8037 | 0.95 ( 0.63, | 1.44) | 0.95 ( 0.62, | 1.46) | 0.00 (-0.02, 0.01) | |
| 75 to <85 | 1033 | 41 | 4.0 | 1019 | 20 | 2.0 | 0.0075 | 0.49 ( 0.29, | 0.84) | 0.48 ( 0.28, | 0.83) | -0.02 (-0.03,-0.01) | |
| >=85 | 986 | 24 | 2.4 | 991 | 30 | 3.0 | 0.4185 | 1.24 ( 0.73, | 2.11) | 1.25 ( 0.73, | 2.16) | 0.01 (-0.01, 0.02) | |
| History of heart failure | | | | | | | | | | | | | 0.0790 |
| No | 2970 | 93 | 3.1 | 2979 | 86 | 2.9 | 0.5811 | 0.92 ( 0.69, | 1.23) | 0.92 ( 0.68, | 1.24) | 0.00 (-0.01, 0.01) | |
| Yes | 334 | 16 | 4.8 | 324 | 6 | 1.9 | 0.0361 | 0.39 ( 0.15, | 0.98) | 0.38 ( 0.14, | 0.97) | -0.03 (-0.06, 0.00) | |
| History of renal disease | | | | | | | | | | | | | 0.8591 |
| Diabetic kidney disease | 1025 | 38 | 3.7 | 1032 | 30 | 2.9 | 0.3100 | 0.78 ( 0.49, | 1.26) | 0.78 ( 0.48, | 1.27) | -0.01 (-0.02, 0.01) | |
| Glomerular disease | 816 | 20 | 2.5 | 853 | 15 | 1.8 | 0.3237 | 0.72 ( 0.37, | 1.39) | 0.71 ( 0.36, | 1.40) | -0.01 (-0.02, 0.01) | |
| Hypertensive/renovascular disease | 739 | 25 | 3.4 | 706 | 24 | 3.4 | 0.9862 | 1.00 ( 0.58, | 1.74) | 1.01 ( 0.57, | 1.78) | 0.00 (-0.02, 0.02) | |
| Other/Unknown | 725 | 26 | 3.6 | 713 | 23 | 3.2 | 0.7064 | 0.90 ( 0.52, | 1.56) | 0.90 ( 0.51, | 1.59) | 0.00 (-0.02, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.8932 |
| <30 | 1151 | 65 | 5.6 | 1131 | 53 | 4.7 | 0.2999 | 0.83 ( 0.58, | 1.18) | 0.82 ( 0.57, | 1.19) | -0.01 (-0.03, 0.01) | |
| 30 to <45 | 1461 | 37 | 2.5 | 1467 | 34 | 2.3 | 0.7055 | 0.92 ( 0.58, | 1.45) | 0.91 ( 0.57, | 1.46) | 0.00 (-0.01, 0.01) | |
| >=45 | 693 | 7 | 1.0 | 706 | 5 | 0.7 | 0.5404 | 0.70 ( 0.22, | 2.20) | 0.70 ( 0.22, | 2.21) | 0.00 (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.9463 |
| Normal (<30) | 663 | 16 | 2.4 | 665 | 14 | 2.1 | 0.7057 | 0.87 ( 0.43, | 1.77) | 0.87 ( 0.42, | 1.80) | 0.00 (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 31 | 3.3 | 927 | 24 | 2.6 | 0.3588 | 0.78 ( 0.46, | 1.32) | 0.78 ( 0.45, | 1.33) | -0.01 (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 62 | 3.6 | 1712 | 54 | 3.2 | 0.4365 | 0.87 ( 0.61, | 1.24) | 0.86 ( 0.60, | 1.25) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9569 |
| Low, moderate or high | 833 | 8 | 1.0 | 839 | 7 | 0.8 | 0.7846 | 0.87 ( 0.32, | 2.38) | 0.87 ( 0.31, | 2.40) | 0.00 (-0.01, | 0.01) | |
| Very high | 2472 | 101 | 4.1 | 2465 | 85 | 3.4 | 0.2395 | 0.84 ( 0.64, | 1.12) | 0.84 ( 0.62, | 1.13) | -0.01 (-0.02, | 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.2999 |
| No | 508 | 17 | 3.3 | 473 | 9 | 1.9 | 0.1595 | 0.57 ( 0.26, | 1.26) | 0.56 ( 0.25, | 1.27) | -0.01 (-0.03, | 0.01) | |
| Yes | 2797 | 92 | 3.3 | 2831 | 83 | 2.9 | 0.4399 | 0.89 ( 0.67, | 1.19) | 0.89 ( 0.66, | 1.20) | 0.00 (-0.01, | 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7540 |
| No | 1940 | 52 | 2.7 | 1908 | 45 | 2.4 | 0.5242 | 0.88 ( 0.59, | 1.30) | 0.88 ( 0.59, | 1.31) | 0.00 (-0.01, | 0.01) | |
| Yes | 1365 | 57 | 4.2 | 1396 | 47 | 3.4 | 0.2643 | 0.81 ( 0.55, | 1.18) | 0.80 ( 0.54, | 1.19) | -0.01 (-0.02, | 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4896 |
| No | 1852 | 65 | 3.5 | 1942 | 53 | 2.7 | 0.1662 | 0.78 ( 0.54, | 1.11) | 0.77 ( 0.53, | 1.12) | -0.01 (-0.02, | 0.00) | |
| Yes | 1453 | 44 | 3.0 | 1362 | 39 | 2.9 | 0.7962 | 0.95 ( 0.62, | 1.45) | 0.94 ( 0.61, | 1.46) | 0.00 (-0.01, | 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 3305 | 77 | 2.3 | 3304 | 77 | 2.3 | 0.9985 | 1.00 ( 0.73, 1.37) | 1.00 ( 0.73, 1.38) | 0.00 (-0.01, 0.01) | | |
| Sex | | | | | | | | | | | | 0.7319 |
| Male | 2210 | 45 | 2.0 | 2207 | 47 | 2.1 | 0.8280 | 1.05 ( 0.70, 1.57) | 1.05 ( 0.69, 1.58) | 0.00 (-0.01, 0.01) | | |
| Female | 1095 | 32 | 2.9 | 1097 | 30 | 2.7 | 0.7910 | 0.94 ( 0.57, 1.53) | 0.93 ( 0.56, 1.55) | 0.00 (-0.02, 0.01) | | |
| Age [years] | | | | | | | | | | | | 0.2919 |
| <65 | 1501 | 27 | 1.8 | 1501 | 21 | 1.4 | 0.3826 | 0.78 ( 0.44, 1.37) | 0.77 ( 0.44, 1.38) | 0.00 (-0.01, 0.00) | | |
| >=65 | 1804 | 50 | 2.8 | 1803 | 56 | 3.1 | 0.5522 | 1.12 ( 0.77, 1.63) | 1.12 ( 0.76, 1.66) | 0.00 (-0.01, 0.01) | | |
| Region | | | | | | | | | | | | 0.5366 |
| North America | 873 | 37 | 4.2 | 844 | 34 | 4.0 | 0.8272 | 0.95 ( 0.60, 1.50) | 0.95 ( 0.59, 1.53) | 0.00 (-0.02, 0.02) | | |
| Europe | 1304 | 28 | 2.1 | 1344 | 24 | 1.8 | 0.5027 | 0.83 ( 0.48, 1.43) | 0.83 ( 0.48, 1.44) | 0.00 (-0.01, 0.01) | | |
| Japan | 308 | 6 | 1.9 | 304 | 10 | 3.3 | 0.2984 | 1.69 ( 0.62, 4.59) | 1.71 ( 0.61, 4.77) | 0.01 (-0.01, 0.04) | | |
| Other Asia | 820 | 6 | 0.7 | 812 | 9 | 1.1 | 0.4253 | 1.51 ( 0.54, 4.24) | 1.52 ( 0.54, 4.29) | 0.00 (-0.01, 0.01) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1310 |
| Diabetic | 1515 | 77 | 5.1 | 1525 | 73 | 4.8 | 0.7067 | 0.94 ( 0.69, 1.29) | 0.94 ( 0.68, 1.30) | 0.00 (-0.02, 0.01) | | |
| Non-diabetic | 1790 | 0 | 0 | 1779 | 4 | 0.2 | 0.0723 | 9.06 ( 0.49,168.07) | 9.08 ( 0.49,168.70) | 0.00 ( 0.00, 0.00) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.3434 |
| <30 | 1961 | 28 | 1.4 | 1955 | 34 | 1.7 | 0.4352 | 1.22 ( 0.74, 2.00) | 1.22 ( 0.74, 2.02) | 0.00 ( 0.00, 0.01) | | |
| >=30 | 1337 | 48 | 3.6 | 1340 | 43 | 3.2 | 0.5863 | 0.89 ( 0.60, 1.34) | 0.89 ( 0.59, 1.35) | 0.00 (-0.02, 0.01) | | |
| Prior CV disease | | | | | | | | | | | | 0.4324 |
| No | 2401 | 41 | 1.7 | 2443 | 47 | 1.9 | 0.5731 | 1.13 ( 0.74, 1.71) | 1.13 ( 0.74, 1.72) | 0.00 (-0.01, 0.01) | | |
| Yes | 904 | 36 | 4.0 | 861 | 30 | 3.5 | 0.5815 | 0.87 ( 0.54, 1.41) | 0.87 ( 0.53, 1.43) | 0.00 (-0.02, 0.01) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0747 |
| <130 | 1208 | 21 | 1.7 | 1190 | 31 | 2.6 | 0.1452 | 1.50 ( 0.87, 2.59) | 1.51 ( 0.86, 2.65) | 0.01 ( 0.00, 0.02) | | |
| >=130 | 2097 | 56 | 2.7 | 2114 | 46 | 2.2 | 0.2966 | 0.81 ( 0.55, 1.20) | 0.81 ( 0.55, 1.20) | 0.00 (-0.01, 0.00) | | |

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$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5552 |
| <75 | 1286 | 47 | 3.7 | 1294 | 44 | 3.4 | 0.7261 | 0.93 ( 0.62, 1.39) | 0.93 ( 0.61, 1.41) | 0.00 | (-0.02, 0.01) | |
| 75 to <85 | 1033 | 20 | 1.9 | 1019 | 18 | 1.8 | 0.7756 | 0.91 ( 0.49, 1.71) | 0.91 ( 0.48, 1.73) | 0.00 | (-0.01, 0.01) | |
| >=85 | 986 | 10 | 1.0 | 991 | 15 | 1.5 | 0.3204 | 1.49 ( 0.67, 3.31) | 1.50 ( 0.67, 3.36) | 0.00 | ( 0.00, 0.01) | |
| History of heart failure | | | | | | | | | | | | 0.4096 |
| No | 2970 | 63 | 2.1 | 2979 | 67 | 2.2 | 0.7359 | 1.06 ( 0.75, 1.49) | 1.06 ( 0.75, 1.50) | 0.00 | (-0.01, 0.01) | |
| Yes | 334 | 14 | 4.2 | 324 | 10 | 3.1 | 0.4496 | 0.74 ( 0.33, 1.63) | 0.73 ( 0.32, 1.66) | -0.01 | (-0.04, 0.02) | |
| History of renal disease | | | | | | | | | | | | 0.3389 |
| Diabetic kidney disease | 1025 | 55 | 5.4 | 1032 | 57 | 5.5 | 0.8750 | 1.03 ( 0.72, 1.48) | 1.03 ( 0.70, 1.51) | 0.00 | (-0.02, 0.02) | |
| Glomerular disease | 816 | 2 | 0.2 | 853 | 5 | 0.6 | 0.2811 | 2.39 ( 0.47, 12.29) | 2.40 ( 0.46, 12.40) | 0.00 | ( 0.00, 0.01) | |
| Hypertensive/renovascular disease | 739 | 10 | 1.4 | 706 | 4 | 0.6 | 0.1270 | 0.42 ( 0.13, 1.33) | 0.42 ( 0.13, 1.33) | -0.01 | (-0.02, 0.00) | |
| Other/Unknown | 725 | 10 | 1.4 | 713 | 11 | 1.5 | 0.7961 | 1.12 ( 0.48, 2.62) | 1.12 ( 0.47, 2.65) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1317 |
| <30 | 1151 | 37 | 3.2 | 1131 | 29 | 2.6 | 0.3539 | 0.80 ( 0.49, 1.29) | 0.79 ( 0.48, 1.30) | -0.01 | (-0.02, 0.01) | |
| 30 to <45 | 1461 | 35 | 2.4 | 1467 | 35 | 2.4 | 0.9862 | 1.00 ( 0.63, 1.58) | 1.00 ( 0.62, 1.60) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 5 | 0.7 | 706 | 13 | 1.8 | 0.0631 | 2.55 ( 0.91, 7.12) | 2.58 ( 0.92, 7.28) | 0.01 | ( 0.00, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8144 |
| Normal (<30) | 663 | 13 | 2.0 | 665 | 14 | 2.1 | 0.8520 | 1.07 ( 0.51, 2.27) | 1.08 ( 0.50, 2.31) | 0.00 | (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 29 | 3.1 | 927 | 25 | 2.7 | 0.6084 | 0.87 ( 0.51, 1.48) | 0.87 ( 0.50, 1.49) | 0.00 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 35 | 2.1 | 1712 | 38 | 2.2 | 0.7359 | 1.08 ( 0.69, 1.70) | 1.08 ( 0.68, 1.72) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3844 |
| Low, moderate or high | 833 | 10 | 1.2 | 839 | 14 | 1.7 | 0.4210 | 1.39 ( 0.62, 3.11) | 1.40 ( 0.62, 3.16) | 0.00 | (-0.01, 0.02) | |
| Very high | 2472 | 67 | 2.7 | 2465 | 63 | 2.6 | 0.7345 | 0.94 ( 0.67, 1.32) | 0.94 ( 0.66, 1.33) | 0.00 | (-0.01, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | 0.6786 |
| No | 508 | 14 | 2.8 | 473 | 15 | 3.2 | 0.7011 | 1.15 ( 0.56, 2.36) | 1.16 ( 0.55, 2.42) | 0.00 | (-0.02, 0.03) | |
| Yes | 2797 | 63 | 2.3 | 2831 | 62 | 2.2 | 0.8739 | 0.97 ( 0.69, 1.38) | 0.97 ( 0.68, 1.39) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3919 |
| No | 1940 | 40 | 2.1 | 1908 | 34 | 1.8 | 0.5273 | 0.86 ( 0.55, 1.36) | 0.86 ( 0.54, 1.37) | 0.00 | (-0.01, 0.01) | |
| Yes | 1365 | 37 | 2.7 | 1396 | 43 | 3.1 | 0.5627 | 1.14 ( 0.74, 1.75) | 1.14 ( 0.73, 1.78) | 0.00 | (-0.01, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.0011 |
| No | 1852 | 14 | 0.8 | 1942 | 35 | 1.8 | 0.0043 | 2.38 ( 1.29, 4.42) | 2.41 ( 1.29, 4.49) | 0.01 | ( 0.00, 0.02) | |
| Yes | 1453 | 63 | 4.3 | 1362 | 42 | 3.1 | 0.0798 | 0.71 ( 0.48, 1.04) | 0.70 ( 0.47, 1.04) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
$Only severe events are included. *** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: ^Lower limb amputations (adjudicated)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 17 | 0.5 | 3304 | 26 | 0.8 | 0.1682 | 1.53 | ( 0.83, 2.81) | 1.53 | ( 0.83, 2.83) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.5013 |
| Male | 2210 | 13 | 0.6 | 2207 | 22 | 1.0 | 0.1257 | 1.69 | ( 0.86, 3.36) | 1.70 | ( 0.86, 3.39) | 0.00 | ( 0.00, 0.01) | |
| Female | 1095 | 4 | 0.4 | 1097 | 4 | 0.4 | 0.9979 | 1.00 | ( 0.25, 3.98) | 1.00 | ( 0.25, 4.00) | 0.00 | (-0.01, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6622 |
| <65 | 1501 | 7 | 0.5 | 1501 | 9 | 0.6 | 0.6161 | 1.29 | ( 0.48, 3.44) | 1.29 | ( 0.48, 3.47) | 0.00 | ( 0.00, 0.01) | |
| >=65 | 1804 | 10 | 0.6 | 1803 | 17 | 0.9 | 0.1758 | 1.70 | ( 0.78, 3.70) | 1.71 | ( 0.78, 3.74) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.2240 |
| North America | 873 | 8 | 0.9 | 844 | 5 | 0.6 | 0.4388 | 0.65 | ( 0.21, 1.97) | 0.64 | ( 0.21, 1.98) | 0.00 | (-0.01, 0.00) | |
| Europe | 1304 | 7 | 0.5 | 1344 | 11 | 0.8 | 0.3779 | 1.52 | ( 0.59, 3.92) | 1.53 | ( 0.59, 3.96) | 0.00 | ( 0.00, 0.01) | |
| Japan | 308 | 0 | 0 | 304 | 2 | 0.7 | 0.2425 | 5.07 | ( 0.24,105.08) | 5.10 | ( 0.24,106.65) | 0.01 | ( 0.00, 0.02) | |
| Other Asia | 820 | 2 | 0.2 | 812 | 8 | 1.0 | 0.0550 | 4.04 | ( 0.86, 18.96) | 4.07 | ( 0.86, 19.22) | 0.01 | ( 0.00, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5324 |
| Diabetic | 1515 | 16 | 1.1 | 1525 | 23 | 1.5 | 0.2681 | 1.43 | ( 0.76, 2.69) | 1.43 | ( 0.75, 2.73) | 0.00 | ( 0.00, 0.01) | |
| Non-diabetic | 1790 | 1 | 0.1 | 1779 | 3 | 0.2 | 0.3141 | 3.02 | ( 0.31, 28.99) | 3.02 | ( 0.31, 29.08) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6564 |
| <30 | 1961 | 8 | 0.4 | 1955 | 14 | 0.7 | 0.1970 | 1.76 | ( 0.74, 4.17) | 1.76 | ( 0.74, 4.21) | 0.00 | ( 0.00, 0.01) | |
| >=30 | 1337 | 9 | 0.7 | 1340 | 12 | 0.9 | 0.5143 | 1.33 | ( 0.56, 3.15) | 1.33 | ( 0.56, 3.17) | 0.00 | ( 0.00, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | 0.5463 |
| No | 2401 | 6 | 0.2 | 2443 | 12 | 0.5 | 0.1676 | 1.97 | ( 0.74, 5.23) | 1.97 | ( 0.74, 5.26) | 0.00 | ( 0.00, 0.01) | |
| Yes | 904 | 11 | 1.2 | 861 | 14 | 1.6 | 0.4671 | 1.34 | ( 0.61, 2.93) | 1.34 | ( 0.61, 2.97) | 0.00 | (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4580 |
| <130 | 1208 | 6 | 0.5 | 1190 | 12 | 1.0 | 0.1466 | 2.03 | ( 0.76, 5.39) | 2.04 | ( 0.76, 5.46) | 0.01 | ( 0.00, 0.01) | |
| >=130 | 2097 | 11 | 0.5 | 2114 | 14 | 0.7 | 0.5609 | 1.26 | ( 0.57, 2.77) | 1.26 | ( 0.57, 2.79) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
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For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
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Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: ^Lower limb amputations (adjudicated)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1812 |
| <75 | 1286 | 12 | 0.9 | 1294 | 15 | 1.2 | 0.5726 | 1.24 | ( 0.58, 2.64) | 1.25 | ( 0.58, 2.67) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1033 | 4 | 0.4 | 1019 | 3 | 0.3 | 0.7184 | 0.76 | ( 0.17, 3.39) | 0.76 | ( 0.17, 3.40) | 0.00 | (-0.01, 0.00) | |
| >=85 | 986 | 1 | 0.1 | 991 | 8 | 0.8 | 0.0197 | 7.96 | (<1.00, 63.52) | 8.02 | ( 1.00, 64.21) | 0.01 | ( 0.00, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.3232 |
| No | 2970 | 13 | 0.4 | 2979 | 23 | 0.8 | 0.0964 | 1.76 | ( 0.90, 3.48) | 1.77 | ( 0.89, 3.50) | 0.00 | ( 0.00, 0.01) | |
| Yes | 334 | 4 | 1.2 | 324 | 3 | 0.9 | 0.7342 | 0.77 | ( 0.17, 3.43) | 0.77 | ( 0.17, 3.47) | 0.00 | (-0.02, 0.01) | |
| History of renal disease | | | | | | | | | | | | | | 0.8000 |
| Diabetic kidney disease | 1025 | 12 | 1.2 | 1032 | 21 | 2.0 | 0.1188 | 1.74 | ( 0.86, 3.51) | 1.75 | ( 0.86, 3.58) | 0.01 | ( 0.00, 0.02) | |
| Glomerular disease | 816 | 1 | 0.1 | 853 | 1 | 0.1 | 0.9750 | 0.96 | ( 0.06, 15.27) | 0.96 | ( 0.06, 15.32) | 0.00 | ( 0.00, 0.00) | |
| Hypertensive/renovascular disease | 739 | 2 | 0.3 | 706 | 1 | 0.1 | 0.5902 | 0.52 | ( 0.05, 5.76) | 0.52 | ( 0.05, 5.78) | 0.00 | (-0.01, 0.00) | |
| Other/Unknown | 725 | 2 | 0.3 | 713 | 3 | 0.4 | 0.6407 | 1.53 | ( 0.26, 9.10) | 1.53 | ( 0.25, 9.17) | 0.00 | ( 0.00, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7357 |
| <30 | 1151 | 8 | 0.7 | 1131 | 11 | 1.0 | 0.4657 | 1.40 | ( 0.56, 3.47) | 1.40 | ( 0.56, 3.50) | 0.00 | ( 0.00, 0.01) | |
| 30 to <45 | 1461 | 6 | 0.4 | 1467 | 12 | 0.8 | 0.1586 | 1.99 | ( 0.75, 5.29) | 2.00 | ( 0.75, 5.34) | 0.00 | ( 0.00, 0.01) | |
| >=45 | 693 | 3 | 0.4 | 706 | 3 | 0.4 | 0.9818 | 0.98 | ( 0.20, 4.85) | 0.98 | ( 0.20, 4.88) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7924 |
| Normal (<30) | 663 | 4 | 0.6 | 665 | 4 | 0.6 | 0.9966 | 1.00 | ( 0.25, 3.97) | 1.00 | ( 0.25, 4.00) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 5 | 0.5 | 927 | 8 | 0.9 | 0.3929 | 1.62 | ( 0.53, 4.93) | 1.62 | ( 0.53, 4.98) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 8 | 0.5 | 1712 | 14 | 0.8 | 0.2028 | 1.74 | ( 0.73, 4.14) | 1.75 | ( 0.73, 4.18) | 0.00 | ( 0.00, 0.01) | |

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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: ^Lower limb amputations (adjudicated)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.8346 |
| Low, moderate or high | 833 | 3 | 0.4 | 839 | 4 | 0.5 | 0.7119 | 1.32 | ( 0.30, | 5.90) | 1.33 | ( 0.30, | 5.94) | 0.00 | (-0.01, 0.01) | |
| Very high | 2472 | 14 | 0.6 | 2465 | 22 | 0.9 | 0.1781 | 1.58 | ( 0.81, | 3.07) | 1.58 | ( 0.81, | 3.10) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | | 0.9228 |
| No | 508 | 3 | 0.6 | 473 | 4 | 0.8 | 0.6352 | 1.43 | ( 0.32, | 6.36) | 1.44 | ( 0.32, | 6.45) | 0.00 | (-0.01, 0.01) | |
| Yes | 2797 | 14 | 0.5 | 2831 | 22 | 0.8 | 0.1932 | 1.55 | ( 0.80, | 3.03) | 1.56 | ( 0.79, | 3.05) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.1654 |
| No | 1940 | 5 | 0.3 | 1908 | 13 | 0.7 | 0.0542 | 2.64 | ( 0.94, | 7.40) | 2.65 | ( 0.94, | 7.46) | 0.00 | ( 0.00, 0.01) | |
| Yes | 1365 | 12 | 0.9 | 1396 | 13 | 0.9 | 0.8851 | 1.06 | ( 0.49, | 2.31) | 1.06 | ( 0.48, | 2.33) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.3013 |
| No | 1852 | 6 | 0.3 | 1942 | 6 | 0.3 | 0.9344 | 0.95 | ( 0.31, | 2.95) | 0.95 | ( 0.31, | 2.96) | 0.00 | ( 0.00, 0.00) | |
| Yes | 1453 | 11 | 0.8 | 1362 | 20 | 1.5 | 0.0707 | 1.94 | ( 0.93, | 4.03) | 1.95 | ( 0.93, | 4.09) | 0.01 | ( 0.00, 0.01) | |

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For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 18 | 0.5 | 3304 | 15 | 0.5 | 0.6012 | 0.83 | ( 0.42, | 1.65) | 0.83 | ( 0.42, | 1.66) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.4568 |
| Male | 2210 | 11 | 0.5 | 2207 | 11 | 0.5 | 0.9975 | 1.00 | ( 0.44, | 2.30) | 1.00 | ( 0.43, | 2.31) | 0.00 | ( 0.00, 0.00) | |
| Female | 1095 | 7 | 0.6 | 1097 | 4 | 0.4 | 0.3629 | 0.57 | ( 0.17, | 1.94) | 0.57 | ( 0.17, | 1.95) | 0.00 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | | | 0.5151 |
| <65 | 1501 | 8 | 0.5 | 1501 | 5 | 0.3 | 0.4044 | 0.63 | ( 0.20, | 1.91) | 0.62 | ( 0.20, | 1.91) | 0.00 | (-0.01, 0.00) | |
| >=65 | 1804 | 10 | 0.6 | 1803 | 10 | 0.6 | 0.9990 | 1.00 | ( 0.42, | 2.40) | 1.00 | ( 0.42, | 2.41) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | | | 0.6119 |
| North America | 873 | 5 | 0.6 | 844 | 6 | 0.7 | 0.7198 | 1.24 | ( 0.38, | 4.05) | 1.24 | ( 0.38, | 4.09) | 0.00 | (-0.01, 0.01) | |
| Europe | 1304 | 7 | 0.5 | 1344 | 5 | 0.4 | 0.5279 | 0.69 | ( 0.22, | 2.18) | 0.69 | ( 0.22, | 2.19) | 0.00 | (-0.01, 0.00) | |
| Japan | 308 | 1 | 0.3 | 304 | 2 | 0.7 | 0.5551 | 2.03 | ( 0.18, | 22.23) | 2.03 | ( 0.18, | 22.54) | 0.00 | (-0.01, 0.01) | |
| Other Asia | 820 | 5 | 0.6 | 812 | 2 | 0.2 | 0.2613 | 0.40 | ( 0.08, | 2.08) | 0.40 | ( 0.08, | 2.08) | 0.00 | (-0.01, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | | 0.9559 |
| Diabetic | 1515 | 13 | 0.9 | 1525 | 11 | 0.7 | 0.6701 | 0.84 | ( 0.38, | 1.87) | 0.84 | ( 0.37, | 1.88) | 0.00 | (-0.01, 0.00) | |
| Non-diabetic | 1790 | 5 | 0.3 | 1779 | 4 | 0.2 | 0.7456 | 0.80 | ( 0.22, | 2.99) | 0.80 | ( 0.22, | 3.00) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.4400 |
| <30 | 1961 | 12 | 0.6 | 1955 | 8 | 0.4 | 0.3735 | 0.67 | ( 0.27, | 1.63) | 0.67 | ( 0.27, | 1.64) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1337 | 6 | 0.4 | 1340 | 7 | 0.5 | 0.7841 | 1.16 | ( 0.39, | 3.45) | 1.16 | ( 0.39, | 3.48) | 0.00 | ( 0.00, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | | | 0.5761 |
| No | 2401 | 10 | 0.4 | 2443 | 10 | 0.4 | 0.9690 | 0.98 | ( 0.41, | 2.36) | 0.98 | ( 0.41, | 2.37) | 0.00 | ( 0.00, 0.00) | |
| Yes | 904 | 8 | 0.9 | 861 | 5 | 0.6 | 0.4550 | 0.66 | ( 0.22, | 2.00) | 0.65 | ( 0.21, | 2.01) | 0.00 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.2598 |
| <130 | 1208 | 4 | 0.3 | 1190 | 6 | 0.5 | 0.5108 | 1.52 | ( 0.43, | 5.38) | 1.53 | ( 0.43, | 5.42) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 2097 | 14 | 0.7 | 2114 | 9 | 0.4 | 0.2869 | 0.64 | ( 0.28, | 1.47) | 0.64 | ( 0.27, | 1.47) | 0.00 | (-0.01, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.8138 |
| <75 | 1286 | 11 | 0.9 | 1294 | 10 | 0.8 | 0.8155 | 0.90 | ( 0.39, | 2.12) | 0.90 | ( 0.38, | 2.13) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1033 | 4 | 0.4 | 1019 | 2 | 0.2 | 0.4231 | 0.51 | ( 0.09, | 2.76) | 0.51 | ( 0.09, | 2.77) | 0.00 | (-0.01, 0.00) | |
| >=85 | 986 | 3 | 0.3 | 991 | 3 | 0.3 | 0.9950 | 0.99 | ( 0.20, | 4.92) | 0.99 | ( 0.20, | 4.94) | 0.00 | ( 0.00, 0.00) | |
| History of heart failure | | | | | | | | | | | | | | | | 0.5351 |
| No | 2970 | 14 | 0.5 | 2979 | 13 | 0.4 | 0.8409 | 0.93 | ( 0.44, | 1.97) | 0.93 | ( 0.43, | 1.97) | 0.00 | ( 0.00, 0.00) | |
| Yes | 334 | 4 | 1.2 | 324 | 2 | 0.6 | 0.4337 | 0.52 | ( 0.10, | 2.79) | 0.51 | ( 0.09, | 2.82) | -0.01 | (-0.02, 0.01) | |
| History of renal disease | | | | | | | | | | | | | | | | 0.9574 |
| Diabetic kidney disease | 1025 | 10 | 1.0 | 1032 | 9 | 0.9 | 0.8062 | 0.89 | ( 0.36, | 2.19) | 0.89 | ( 0.36, | 2.21) | 0.00 | (-0.01, 0.01) | |
| Glomerular disease | 816 | 3 | 0.4 | 853 | 2 | 0.2 | 0.6187 | 0.64 | ( 0.11, | 3.81) | 0.64 | ( 0.11, | 3.82) | 0.00 | (-0.01, 0.00) | |
| Hypertensive/renovascular disease | 739 | 2 | 0.3 | 706 | 1 | 0.1 | 0.5902 | 0.52 | ( 0.05, | 5.76) | 0.52 | ( 0.05, | 5.78) | 0.00 | (-0.01, 0.00) | |
| Other/Unknown | 725 | 3 | 0.4 | 713 | 3 | 0.4 | 0.9837 | 1.02 | ( 0.21, | 5.02) | 1.02 | ( 0.20, | 5.06) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.7221 |
| <30 | 1151 | 9 | 0.8 | 1131 | 6 | 0.5 | 0.4574 | 0.68 | ( 0.24, | 1.90) | 0.68 | ( 0.24, | 1.91) | 0.00 | (-0.01, 0.00) | |
| 30 to <45 | 1461 | 8 | 0.5 | 1467 | 7 | 0.5 | 0.7896 | 0.87 | ( 0.32, | 2.40) | 0.87 | ( 0.31, | 2.41) | 0.00 | (-0.01, 0.00) | |
| >=45 | 693 | 1 | 0.1 | 706 | 2 | 0.3 | 0.5742 | 1.96 | ( 0.18, | 21.60) | 1.97 | ( 0.18, | 21.73) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.2994 |
| Normal (<30) | 663 | 3 | 0.5 | 665 | 1 | 0.2 | 0.3151 | 0.33 | ( 0.03, | 3.19) | 0.33 | ( 0.03, | 3.19) | 0.00 | (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 937 | 5 | 0.5 | 927 | 8 | 0.9 | 0.3929 | 1.62 | ( 0.53, | 4.93) | 1.62 | ( 0.53, | 4.98) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 10 | 0.6 | 1712 | 6 | 0.4 | 0.3122 | 0.60 | ( 0.22, | 1.64) | 0.60 | ( 0.22, | 1.64) | 0.00 | (-0.01, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2363 |
| Low, moderate or high | 833 | 1 | 0.1 | 839 | 3 | 0.4 | 0.3202 | 2.98 | ( 0.31, 28.58) | 2.99 | ( 0.31, 28.76) | 0.00 | ( 0.00, 0.01) | |
| Very high | 2472 | 17 | 0.7 | 2465 | 12 | 0.5 | 0.3557 | 0.71 | ( 0.34, 1.48) | 0.71 | ( 0.34, 1.48) | 0.00 | (-0.01, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.0745 |
| No | 508 | 6 | 1.2 | 473 | 0 | 0 | 0.0291 | 0.08 | (<0.01, 1.46) | 0.08 | (<0.01, 1.45) | -0.01 | (-0.02, 0.00) | |
| Yes | 2797 | 12 | 0.4 | 2831 | 15 | 0.5 | 0.5842 | 1.23 | ( 0.58, 2.63) | 1.24 | ( 0.58, 2.65) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3098 |
| No | 1940 | 9 | 0.5 | 1908 | 10 | 0.5 | 0.7900 | 1.13 | ( 0.46, 2.77) | 1.13 | ( 0.46, 2.79) | 0.00 | ( 0.00, 0.01) | |
| Yes | 1365 | 9 | 0.7 | 1396 | 5 | 0.4 | 0.2653 | 0.54 | ( 0.18, 1.62) | 0.54 | ( 0.18, 1.62) | 0.00 | (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6279 |
| No | 1852 | 7 | 0.4 | 1942 | 5 | 0.3 | 0.5088 | 0.68 | ( 0.22, 2.14) | 0.68 | ( 0.22, 2.15) | 0.00 | ( 0.00, 0.00) | |
| Yes | 1453 | 11 | 0.8 | 1362 | 10 | 0.7 | 0.9439 | 0.97 | ( 0.41, 2.28) | 0.97 | ( 0.41, 2.29) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 1 | <0.1 | 3304 | 6 | 0.2 | 0.0586 | 6.00 | ( 0.72, 49.82) | 6.01 | ( 0.72, 49.96) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | |
| Male | 2210 | 1 | <0.1 | 2207 | 3 | 0.1 | | | | | | | |
| Female | 1095 | 0 | 0 | 1097 | 3 | 0.3 | | | | | | | |
| Age [years] | | | | | | | | | | | | | |
| <65 | 1501 | 0 | 0 | 1501 | 4 | 0.3 | | | | | | | |
| >=65 | 1804 | 1 | 0.1 | 1803 | 2 | 0.1 | | | | | | | |
| Region | | | | | | | | | | | | | |
| North America | 873 | 1 | 0.1 | 844 | 2 | 0.2 | | | | | | | |
| Europe | 1304 | 0 | 0 | 1344 | 2 | 0.1 | | | | | | | |
| Japan | 308 | 0 | 0 | 304 | 0 | 0 | | | | | | | |
| Other Asia | 820 | 0 | 0 | 812 | 2 | 0.2 | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | |
| Diabetic | 1515 | 1 | 0.1 | 1525 | 5 | 0.3 | | | | | | | |
| Non-diabetic | 1790 | 0 | 0 | 1779 | 1 | 0.1 | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | |
| <30 | 1961 | 0 | 0 | 1955 | 3 | 0.2 | | | | | | | |
| >=30 | 1337 | 1 | 0.1 | 1340 | 3 | 0.2 | | | | | | | |
| Prior CV disease | | | | | | | | | | | | | |
| No | 2401 | 1 | <0.1 | 2443 | 4 | 0.2 | | | | | | | |
| Yes | 904 | 0 | 0 | 861 | 2 | 0.2 | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | |
| <130 | 1208 | 0 | 0 | 1190 | 3 | 0.3 | | | | | | | |
| >=130 | 2097 | 1 | <0.1 | 2114 | 3 | 0.1 | | | | | | | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 1286 | 1 | 0.1 | 1294 | 4 | 0.3 | | | | | |
| 75 to <85 | 1033 | 0 | 0 | 1019 | 1 | 0.1 | | | | | |
| >=85 | 986 | 0 | 0 | 991 | 1 | 0.1 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 2970 | 1 | <0.1 | 2979 | 4 | 0.1 | | | | | |
| Yes | 334 | 0 | 0 | 324 | 2 | 0.6 | | | | | |
| History of renal disease | | | | | | | | | | | |
| Diabetic kidney disease | 1025 | 1 | 0.1 | 1032 | 5 | 0.5 | | | | | |
| Glomerular disease | 816 | 0 | 0 | 853 | 0 | 0 | | | | | |
| Hypertensive/renovascular disease | 739 | 0 | 0 | 706 | 0 | 0 | | | | | |
| Other/Unknown | 725 | 0 | 0 | 713 | 1 | 0.1 | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 1151 | 0 | 0 | 1131 | 4 | 0.4 | | | | | |
| 30 to <45 | 1461 | 1 | 0.1 | 1467 | 1 | 0.1 | | | | | |
| >=45 | 693 | 0 | 0 | 706 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 663 | 0 | 0 | 665 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 937 | 0 | 0 | 927 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 1705 | 1 | 0.1 | 1712 | 5 | 0.3 | | | | | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 833 | 0 | 0 | 839 | 0 | 0 | | | | | |
| Very high | 2472 | 1 | <0.1 | 2465 | 6 | 0.2 | | | | | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | |
| No | 508 | 0 | 0 | 473 | 0 | 0 | | | | | |
| Yes | 2797 | 1 | <0.1 | 2831 | 6 | 0.2 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 1940 | 0 | 0 | 1908 | 1 | 0.1 | | | | | |
| Yes | 1365 | 1 | 0.1 | 1396 | 5 | 0.4 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 1852 | 0 | 0 | 1942 | 3 | 0.2 | | | | | |
| Yes | 1453 | 1 | 0.1 | 1362 | 3 | 0.2 | | | | | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)$

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 19 | 0.6 | 3304 | 16 | 0.5 | 0.6118 | 0.84 | ( 0.43, 1.64) | 0.84 | ( 0.43, 1.64) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.1465 |
| Male | 2210 | 13 | 0.6 | 2207 | 7 | 0.3 | 0.1797 | 0.54 | ( 0.22, 1.35) | 0.54 | ( 0.21, 1.35) | 0.00 | (-0.01, 0.00) | |
| Female | 1095 | 6 | 0.5 | 1097 | 9 | 0.8 | 0.4391 | 1.50 | ( 0.53, 4.19) | 1.50 | ( 0.53, 4.23) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6671 |
| <65 | 1501 | 6 | 0.4 | 1501 | 4 | 0.3 | 0.5264 | 0.67 | ( 0.19, 2.36) | 0.67 | ( 0.19, 2.36) | 0.00 | (-0.01, 0.00) | |
| >=65 | 1804 | 13 | 0.7 | 1803 | 12 | 0.7 | 0.8420 | 0.92 | ( 0.42, 2.02) | 0.92 | ( 0.42, 2.03) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.8765 |
| North America | 873 | 10 | 1.1 | 844 | 6 | 0.7 | 0.3488 | 0.62 | ( 0.23, 1.70) | 0.62 | ( 0.22, 1.71) | 0.00 | (-0.01, 0.00) | |
| Europe | 1304 | 6 | 0.5 | 1344 | 7 | 0.5 | 0.8232 | 1.13 | ( 0.38, 3.36) | 1.13 | ( 0.38, 3.38) | 0.00 | ( 0.00, 0.01) | |
| Japan | 308 | 1 | 0.3 | 304 | 1 | 0.3 | 0.9926 | 1.01 | ( 0.06, 16.12) | 1.01 | ( 0.06, 16.27) | 0.00 | (-0.01, 0.01) | |
| Other Asia | 820 | 2 | 0.2 | 812 | 2 | 0.2 | 0.9922 | 1.01 | ( 0.14, 7.15) | 1.01 | ( 0.14, 7.19) | 0.00 | ( 0.00, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4192 |
| Diabetic | 1515 | 19 | 1.3 | 1525 | 15 | 1.0 | 0.4782 | 0.78 | ( 0.40, 1.54) | 0.78 | ( 0.40, 1.55) | 0.00 | (-0.01, 0.00) | |
| Non-diabetic | 1790 | 0 | 0 | 1779 | 1 | 0.1 | 0.4767 | 3.02 | ( 0.12, 74.05) | 3.02 | ( 0.12, 74.19) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6864 |
| <30 | 1961 | 8 | 0.4 | 1955 | 6 | 0.3 | 0.5963 | 0.75 | ( 0.26, 2.16) | 0.75 | ( 0.26, 2.17) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1337 | 10 | 0.7 | 1340 | 10 | 0.7 | 0.9960 | 1.00 | ( 0.42, 2.39) | 1.00 | ( 0.41, 2.41) | 0.00 | (-0.01, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | 0.4246 |
| No | 2401 | 9 | 0.4 | 2443 | 10 | 0.4 | 0.8477 | 1.09 | ( 0.44, 2.68) | 1.09 | ( 0.44, 2.69) | 0.00 | ( 0.00, 0.00) | |
| Yes | 904 | 10 | 1.1 | 861 | 6 | 0.7 | 0.3644 | 0.63 | ( 0.23, 1.73) | 0.63 | ( 0.23, 1.73) | 0.00 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0073 |
| <130 | 1208 | 2 | 0.2 | 1190 | 9 | 0.8 | 0.0323 | 4.57 | ( 0.99, 21.10) | 4.60 | ( 0.99, 21.31) | 0.01 | ( 0.00, 0.01) | |
| >=130 | 2097 | 17 | 0.8 | 2114 | 7 | 0.3 | 0.0387 | 0.41 | ( 0.17, 0.98) | 0.41 | ( 0.17, 0.98) | 0.00 | (-0.01, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)$

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5162 |
| <75 | 1286 | 10 | 0.8 | 1294 | 10 | 0.8 | 0.9889 | 0.99 | ( 0.42, 2.38) | 0.99 | ( 0.41, 2.40) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1033 | 8 | 0.8 | 1019 | 4 | 0.4 | 0.2566 | 0.51 | ( 0.15, 1.68) | 0.50 | ( 0.15, 1.68) | 0.00 | (-0.01, 0.00) | |
| >=85 | 986 | 1 | 0.1 | 991 | 2 | 0.2 | 0.5664 | 1.99 | ( 0.18, 21.91) | 1.99 | ( 0.18, 22.00) | 0.00 | ( 0.00, 0.00) | |
| History of heart failure | | | | | | | | | | | | | | 0.8958 |
| No | 2970 | 15 | 0.5 | 2979 | 13 | 0.4 | 0.6988 | 0.86 | ( 0.41, 1.81) | 0.86 | ( 0.41, 1.82) | 0.00 | ( 0.00, 0.00) | |
| Yes | 334 | 4 | 1.2 | 324 | 3 | 0.9 | 0.7342 | 0.77 | ( 0.17, 3.43) | 0.77 | ( 0.17, 3.47) | 0.00 | (-0.02, 0.01) | |
| History of renal disease | | | | | | | | | | | | | | 0.8568 |
| Diabetic kidney disease | 1025 | 17 | 1.7 | 1032 | 13 | 1.3 | 0.4506 | 0.76 | ( 0.37, 1.56) | 0.76 | ( 0.37, 1.57) | 0.00 | (-0.01, 0.01) | |
| Glomerular disease | 816 | 0 | 0 | 853 | 0 | 0 | 0.9823 | 0.96 | ( 0.02, 48.16) | 0.96 | ( 0.02, 48.27) | 0.00 | ( 0.00, 0.00) | |
| Hypertensive/renovascular disease | 739 | 0 | 0 | 706 | 1 | 0.1 | 0.4593 | 3.14 | ( 0.13, 76.95) | 3.14 | ( 0.13, 77.32) | 0.00 | ( 0.00, 0.01) | |
| Other/Unknown | 725 | 2 | 0.3 | 713 | 2 | 0.3 | 0.9867 | 1.02 | ( 0.14, 7.20) | 1.02 | ( 0.14, 7.24) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9787 |
| <30 | 1151 | 9 | 0.8 | 1131 | 7 | 0.6 | 0.6408 | 0.79 | ( 0.30, 2.12) | 0.79 | ( 0.29, 2.13) | 0.00 | (-0.01, 0.01) | |
| 30 to <45 | 1461 | 8 | 0.5 | 1467 | 7 | 0.5 | 0.7896 | 0.87 | ( 0.32, 2.40) | 0.87 | ( 0.31, 2.41) | 0.00 | (-0.01, 0.00) | |
| >=45 | 693 | 2 | 0.3 | 706 | 2 | 0.3 | 0.9852 | 0.98 | ( 0.14, 6.95) | 0.98 | ( 0.14, 6.99) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8139 |
| Normal (<30) | 663 | 3 | 0.5 | 665 | 3 | 0.5 | 0.9970 | 1.00 | ( 0.20, 4.92) | 1.00 | ( 0.20, 4.96) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 8 | 0.9 | 927 | 5 | 0.5 | 0.4147 | 0.63 | ( 0.21, 1.92) | 0.63 | ( 0.21, 1.93) | 0.00 | (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 1705 | 8 | 0.5 | 1712 | 8 | 0.5 | 0.9934 | 1.00 | ( 0.37, 2.65) | 1.00 | ( 0.37, 2.66) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)$

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | 0.8623 |
| Low, moderate or high | 833 | 2 | 0.2 | 839 | 2 | 0.2 | 0.9943 | 0.99 | ( 0.14, | 7.03) | 0.99 | ( 0.14, 7.06) | 0.00 | ( 0.00, 0.00) | |
| Very high | 2472 | 17 | 0.7 | 2465 | 14 | 0.6 | 0.5943 | 0.83 | ( 0.41, | 1.67) | 0.82 | ( 0.41, 1.68) | 0.00 | (-0.01, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | 0.4389 |
| No | 508 | 3 | 0.6 | 473 | 4 | 0.8 | 0.6352 | 1.43 | ( 0.32, | 6.36) | 1.44 | ( 0.32, 6.45) | 0.00 | (-0.01, 0.01) | |
| Yes | 2797 | 16 | 0.6 | 2831 | 12 | 0.4 | 0.4296 | 0.74 | ( 0.35, | 1.56) | 0.74 | ( 0.35, 1.57) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | 0.3622 |
| No | 1940 | 9 | 0.5 | 1908 | 5 | 0.3 | 0.2984 | 0.56 | ( 0.19, | 1.68) | 0.56 | ( 0.19, 1.69) | 0.00 | (-0.01, 0.00) | |
| Yes | 1365 | 10 | 0.7 | 1396 | 11 | 0.8 | 0.8670 | 1.08 | ( 0.46, | 2.52) | 1.08 | ( 0.46, 2.54) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | 0.8155 |
| No | 1852 | 5 | 0.3 | 1942 | 4 | 0.2 | 0.6854 | 0.76 | ( 0.21, | 2.84) | 0.76 | ( 0.20, 2.84) | 0.00 | ( 0.00, 0.00) | |
| Yes | 1453 | 14 | 1.0 | 1362 | 12 | 0.9 | 0.8192 | 0.91 | ( 0.42, | 1.97) | 0.91 | ( 0.42, 1.98) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 54 | 1.6 | 3304 | 52 | 1.6 | 0.8460 | 0.96 | ( 0.66, | 1.41) | 0.96 | ( 0.66, | 1.41) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | | | 0.8753 |
| Male | 2210 | 32 | 1.4 | 2207 | 30 | 1.4 | 0.8023 | 0.94 | ( 0.57, | 1.54) | 0.94 | ( 0.57, | 1.55) | 0.00 | (-0.01, 0.01) | |
| Female | 1095 | 22 | 2.0 | 1097 | 22 | 2.0 | 0.9951 | 1.00 | ( 0.56, | 1.79) | 1.00 | ( 0.55, | 1.81) | 0.00 | (-0.01, 0.01) | |
| Age [years] | | | | | | | | | | | | | | | | 0.2113 |
| <65 | 1501 | 10 | 0.7 | 1501 | 15 | 1.0 | 0.3153 | 1.50 | ( 0.68, | 3.33) | 1.51 | ( 0.67, | 3.36) | 0.00 | ( 0.00, 0.01) | |
| >=65 | 1804 | 44 | 2.4 | 1803 | 37 | 2.1 | 0.4330 | 0.84 | ( 0.55, | 1.30) | 0.84 | ( 0.54, | 1.30) | 0.00 | (-0.01, 0.01) | |
| Region | | | | | | | | | | | | | | | | 0.5251 |
| North America | 873 | 16 | 1.8 | 844 | 17 | 2.0 | 0.7842 | 1.10 | ( 0.56, | 2.16) | 1.10 | ( 0.55, | 2.19) | 0.00 | (-0.01, 0.01) | |
| Europe | 1304 | 30 | 2.3 | 1344 | 24 | 1.8 | 0.3486 | 0.78 | ( 0.46, | 1.32) | 0.77 | ( 0.45, | 1.33) | -0.01 | (-0.02, 0.01) | |
| Japan | 308 | 2 | 0.6 | 304 | 1 | 0.3 | 0.5704 | 0.51 | ( 0.05, | 5.56) | 0.50 | ( 0.05, | 5.60) | 0.00 | (-0.01, 0.01) | |
| Other Asia | 820 | 6 | 0.7 | 812 | 10 | 1.2 | 0.3055 | 1.68 | ( 0.61, | 4.61) | 1.69 | ( 0.61, | 4.68) | 0.00 | ( 0.00, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | | 0.5334 |
| Diabetic | 1515 | 32 | 2.1 | 1525 | 34 | 2.2 | 0.8244 | 1.06 | ( 0.65, | 1.70) | 1.06 | ( 0.65, | 1.72) | 0.00 | (-0.01, 0.01) | |
| Non-diabetic | 1790 | 22 | 1.2 | 1779 | 18 | 1.0 | 0.5376 | 0.82 | ( 0.44, | 1.53) | 0.82 | ( 0.44, | 1.54) | 0.00 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.0532 |
| <30 | 1961 | 32 | 1.6 | 1955 | 21 | 1.1 | 0.1310 | 0.66 | ( 0.38, | 1.14) | 0.65 | ( 0.38, | 1.14) | -0.01 | (-0.01, 0.00) | |
| >=30 | 1337 | 22 | 1.6 | 1340 | 31 | 2.3 | 0.2148 | 1.41 | ( 0.82, | 2.42) | 1.42 | ( 0.82, | 2.46) | 0.01 | ( 0.00, 0.02) | |
| Prior CV disease | | | | | | | | | | | | | | | | 0.3458 |
| No | 2401 | 31 | 1.3 | 2443 | 26 | 1.1 | 0.4641 | 0.82 | ( 0.49, | 1.38) | 0.82 | ( 0.49, | 1.39) | 0.00 | (-0.01, 0.00) | |
| Yes | 904 | 23 | 2.5 | 861 | 26 | 3.0 | 0.5433 | 1.19 | ( 0.68, | 2.06) | 1.19 | ( 0.68, | 2.11) | 0.00 | (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.1066 |
| <130 | 1208 | 17 | 1.4 | 1190 | 24 | 2.0 | 0.2497 | 1.43 | ( 0.77, | 2.65) | 1.44 | ( 0.77, | 2.70) | 0.01 | ( 0.00, 0.02) | |
| >=130 | 2097 | 37 | 1.8 | 2114 | 28 | 1.3 | 0.2469 | 0.75 | ( 0.46, | 1.22) | 0.75 | ( 0.46, | 1.23) | 0.00 | (-0.01, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.8104 |
| <75 | 1286 | 26 | 2.0 | 1294 | 26 | 2.0 | 0.9820 | 0.99 | ( 0.58, | 1.70) | 0.99 | ( 0.57, | 1.72) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1033 | 15 | 1.5 | 1019 | 16 | 1.6 | 0.8264 | 1.08 | ( 0.54, | 2.18) | 1.08 | ( 0.53, | 2.20) | 0.00 | (-0.01, 0.01) | |
| >=85 | 986 | 13 | 1.3 | 991 | 10 | 1.0 | 0.5213 | 0.77 | ( 0.34, | 1.74) | 0.76 | ( 0.33, | 1.75) | 0.00 | (-0.01, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | | | 0.3447 |
| No | 2970 | 44 | 1.5 | 2979 | 38 | 1.3 | 0.4959 | 0.86 | ( 0.56, | 1.33) | 0.86 | ( 0.56, | 1.33) | 0.00 | (-0.01, 0.00) | |
| Yes | 334 | 10 | 3.0 | 324 | 13 | 4.0 | 0.4771 | 1.34 | ( 0.60, | 3.01) | 1.35 | ( 0.59, | 3.13) | 0.01 | (-0.02, 0.04) | |
| History of renal disease | | | | | | | | | | | | | | | | 0.9152 |
| Diabetic kidney disease | 1025 | 20 | 2.0 | 1032 | 23 | 2.2 | 0.6601 | 1.14 | ( 0.63, | 2.07) | 1.15 | ( 0.63, | 2.10) | 0.00 | (-0.01, 0.02) | |
| Glomerular disease | 816 | 8 | 1.0 | 853 | 7 | 0.8 | 0.7296 | 0.84 | ( 0.30, | 2.30) | 0.84 | ( 0.30, | 2.32) | 0.00 | (-0.01, 0.01) | |
| Hypertensive/renovascular disease | 739 | 11 | 1.5 | 706 | 9 | 1.3 | 0.7282 | 0.86 | ( 0.36, | 2.05) | 0.85 | ( 0.35, | 2.07) | 0.00 | (-0.01, 0.01) | |
| Other/Unknown | 725 | 15 | 2.1 | 713 | 13 | 1.8 | 0.7360 | 0.88 | ( 0.42, | 1.84) | 0.88 | ( 0.42, | 1.86) | 0.00 | (-0.02, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.9759 |
| <30 | 1151 | 19 | 1.7 | 1131 | 19 | 1.7 | 0.9565 | 1.02 | ( 0.54, | 1.91) | 1.02 | ( 0.54, | 1.93) | 0.00 | (-0.01, 0.01) | |
| 30 to <45 | 1461 | 30 | 2.1 | 1467 | 28 | 1.9 | 0.7787 | 0.93 | ( 0.56, | 1.55) | 0.93 | ( 0.55, | 1.56) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 5 | 0.7 | 706 | 5 | 0.7 | 0.9765 | 0.98 | ( 0.29, | 3.38) | 0.98 | ( 0.28, | 3.41) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.8004 |
| Normal (<30) | 663 | 12 | 1.8 | 665 | 9 | 1.4 | 0.5049 | 0.75 | ( 0.32, | 1.76) | 0.74 | ( 0.31, | 1.78) | 0.00 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 21 | 2.2 | 927 | 22 | 2.4 | 0.8494 | 1.06 | ( 0.59, | 1.91) | 1.06 | ( 0.58, | 1.94) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 21 | 1.2 | 1712 | 21 | 1.2 | 0.9893 | 1.00 | ( 0.55, | 1.82) | 1.00 | ( 0.54, | 1.83) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | 0.5564 |
| Low, moderate or high | 833 | 8 | 1.0 | 839 | 10 | 1.2 | 0.6465 | 1.24 | ( 0.49, | 3.13) | 1.24 | ( 0.49, 3.17) | 0.00 | (-0.01, 0.01) | |
| Very high | 2472 | 46 | 1.9 | 2465 | 42 | 1.7 | 0.6768 | 0.92 | ( 0.60, | 1.39) | 0.91 | ( 0.60, 1.39) | 0.00 | (-0.01, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | 0.4503 |
| No | 508 | 12 | 2.4 | 473 | 14 | 3.0 | 0.5604 | 1.25 | ( 0.59, | 2.68) | 1.26 | ( 0.58, 2.75) | 0.01 | (-0.01, 0.03) | |
| Yes | 2797 | 42 | 1.5 | 2831 | 38 | 1.3 | 0.6137 | 0.89 | ( 0.58, | 1.38) | 0.89 | ( 0.57, 1.39) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | 0.0251 |
| No | 1940 | 32 | 1.6 | 1908 | 19 | 1.0 | 0.0763 | 0.60 | ( 0.34, | 1.06) | 0.60 | ( 0.34, 1.06) | -0.01 | (-0.01, 0.00) | |
| Yes | 1365 | 22 | 1.6 | 1396 | 33 | 2.4 | 0.1573 | 1.47 | ( 0.86, | 2.50) | 1.48 | ( 0.86, 2.55) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | 0.9032 |
| No | 1852 | 22 | 1.2 | 1942 | 22 | 1.1 | 0.8742 | 0.95 | ( 0.53, | 1.72) | 0.95 | ( 0.53, 1.73) | 0.00 | (-0.01, 0.01) | |
| Yes | 1453 | 32 | 2.2 | 1362 | 30 | 2.2 | 0.9996 | 1.00 | ( 0.61, | 1.64) | 1.00 | ( 0.60, 1.66) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 3 | 0.1 | 3304 | 4 | 0.1 | 0.7050 | 1.33 ( 0.30, 5.95) | 1.33 ( 0.30, 5.97) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 2210 | 3 | 0.1 | 2207 | 3 | 0.1 | | | | | |
| Female | 1095 | 0 | 0 | 1097 | 1 | 0.1 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 1501 | 2 | 0.1 | 1501 | 2 | 0.1 | | | | | |
| >=65 | 1804 | 1 | 0.1 | 1803 | 2 | 0.1 | | | | | |
| Region | | | | | | | | | | | |
| North America | 873 | 0 | 0 | 844 | 1 | 0.1 | | | | | |
| Europe | 1304 | 2 | 0.2 | 1344 | 3 | 0.2 | | | | | |
| Japan | 308 | 0 | 0 | 304 | 0 | 0 | | | | | |
| Other Asia | 820 | 1 | 0.1 | 812 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 1515 | 1 | 0.1 | 1525 | 2 | 0.1 | | | | | |
| Non-diabetic | 1790 | 2 | 0.1 | 1779 | 2 | 0.1 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 1961 | 1 | 0.1 | 1955 | 1 | 0.1 | | | | | |
| >=30 | 1337 | 2 | 0.1 | 1340 | 3 | 0.2 | | | | | |
| Prior CV disease | | | | | | | | | | | |
| No | 2401 | 1 | <0.1 | 2443 | 2 | 0.1 | | | | | |
| Yes | 904 | 2 | 0.2 | 861 | 2 | 0.2 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 1208 | 2 | 0.2 | 1190 | 2 | 0.2 | | | | | |
| >=130 | 2097 | 1 | <0.1 | 2114 | 2 | 0.1 | | | | | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 1286 | 1 | 0.1 | 1294 | 0 | 0 | | | | | |
| 75 to <85 | 1033 | 0 | 0 | 1019 | 3 | 0.3 | | | | | |
| >=85 | 986 | 2 | 0.2 | 991 | 1 | 0.1 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 2970 | 2 | 0.1 | 2979 | 4 | 0.1 | | | | | |
| Yes | 334 | 1 | 0.3 | 324 | 0 | 0 | | | | | |
| History of renal disease | | | | | | | | | | | |
| Diabetic kidney disease | 1025 | 1 | 0.1 | 1032 | 0 | 0 | | | | | |
| Glomerular disease | 816 | 0 | 0 | 853 | 1 | 0.1 | | | | | |
| Hypertensive/renovascular disease | 739 | 1 | 0.1 | 706 | 3 | 0.4 | | | | | |
| Other/Unknown | 725 | 1 | 0.1 | 713 | 0 | 0 | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 1151 | 1 | 0.1 | 1131 | 2 | 0.2 | | | | | |
| 30 to <45 | 1461 | 1 | 0.1 | 1467 | 2 | 0.1 | | | | | |
| >=45 | 693 | 1 | 0.1 | 706 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 663 | 1 | 0.2 | 665 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 937 | 1 | 0.1 | 927 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 1705 | 1 | 0.1 | 1712 | 3 | 0.2 | | | | | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 833 | 1 | 0.1 | 839 | 1 | 0.1 | | | | | |
| Very high | 2472 | 2 | 0.1 | 2465 | 3 | 0.1 | | | | | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | |
| No | 508 | 1 | 0.2 | 473 | 0 | 0 | | | | | |
| Yes | 2797 | 2 | 0.1 | 2831 | 4 | 0.1 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 1940 | 2 | 0.1 | 1908 | 1 | 0.1 | | | | | |
| Yes | 1365 | 1 | 0.1 | 1396 | 3 | 0.2 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 1852 | 1 | 0.1 | 1942 | 1 | 0.1 | | | | | |
| Yes | 1453 | 2 | 0.1 | 1362 | 3 | 0.2 | | | | | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 10 | 0.3 | 3304 | 13 | 0.4 | 0.5304 | 1.30 | ( 0.57, 2.96) | 1.30 | ( 0.57, 2.97) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0569 |
| Male | 2210 | 8 | 0.4 | 2207 | 5 | 0.2 | 0.4061 | 0.63 | ( 0.21, 1.91) | 0.63 | ( 0.20, 1.91) | 0.00 | ( 0.00, 0.00) | |
| Female | 1095 | 2 | 0.2 | 1097 | 8 | 0.7 | 0.0576 | 3.99 | ( 0.85, 18.76) | 4.01 | ( 0.85, 18.95) | 0.01 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6734 |
| <65 | 1501 | 3 | 0.2 | 1501 | 5 | 0.3 | 0.4789 | 1.67 | ( 0.40, 6.96) | 1.67 | ( 0.40, 7.00) | 0.00 | ( 0.00, 0.01) | |
| >=65 | 1804 | 7 | 0.4 | 1803 | 8 | 0.4 | 0.7950 | 1.14 | ( 0.42, 3.15) | 1.14 | ( 0.41, 3.16) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | 0.2253 |
| North America | 873 | 1 | 0.1 | 844 | 4 | 0.5 | 0.1671 | 4.14 | ( 0.46, 36.94) | 4.15 | ( 0.46, 37.23) | 0.00 | ( 0.00, 0.01) | |
| Europe | 1304 | 7 | 0.5 | 1344 | 6 | 0.4 | 0.7394 | 0.83 | ( 0.28, 2.47) | 0.83 | ( 0.28, 2.48) | 0.00 | (-0.01, 0.00) | |
| Japan | 308 | 2 | 0.6 | 304 | 0 | 0 | 0.2517 | 0.20 | (<0.01, 4.20) | 0.20 | (<0.01, 4.21) | -0.01 | (-0.02, 0.00) | |
| Other Asia | 820 | 0 | 0 | 812 | 3 | 0.4 | 0.1306 | 7.07 | ( 0.37,136.63) | 7.10 | ( 0.37,137.58) | 0.00 | ( 0.00, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8665 |
| Diabetic | 1515 | 5 | 0.3 | 1525 | 7 | 0.5 | 0.5707 | 1.39 | ( 0.44, 4.37) | 1.39 | ( 0.44, 4.40) | 0.00 | ( 0.00, 0.01) | |
| Non-diabetic | 1790 | 5 | 0.3 | 1779 | 6 | 0.3 | 0.7549 | 1.21 | ( 0.37, 3.95) | 1.21 | ( 0.37, 3.97) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8595 |
| <30 | 1961 | 5 | 0.3 | 1955 | 6 | 0.3 | 0.7588 | 1.20 | ( 0.37, 3.94) | 1.20 | ( 0.37, 3.95) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1337 | 5 | 0.4 | 1340 | 7 | 0.5 | 0.5655 | 1.40 | ( 0.44, 4.39) | 1.40 | ( 0.44, 4.42) | 0.00 | ( 0.00, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | 0.3127 |
| No | 2401 | 8 | 0.3 | 2443 | 8 | 0.3 | 0.9723 | 0.98 | ( 0.37, 2.61) | 0.98 | ( 0.37, 2.62) | 0.00 | ( 0.00, 0.00) | |
| Yes | 904 | 2 | 0.2 | 861 | 5 | 0.6 | 0.2297 | 2.62 | ( 0.51, 13.49) | 2.63 | ( 0.51, 13.61) | 0.00 | ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3214 |
| <130 | 1208 | 6 | 0.5 | 1190 | 5 | 0.4 | 0.7816 | 0.85 | ( 0.26, 2.76) | 0.85 | ( 0.26, 2.78) | 0.00 | (-0.01, 0.00) | |
| >=130 | 2097 | 4 | 0.2 | 2114 | 8 | 0.4 | 0.2533 | 1.98 | ( 0.60, 6.58) | 1.99 | ( 0.60, 6.61) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6784 |
| <75 | 1286 | 4 | 0.3 | 1294 | 7 | 0.5 | 0.3702 | 1.74 | ( 0.51, 5.93) | 1.74 | ( 0.51, 5.97) | 0.00 | ( 0.00, 0.01) | |
| 75 to <85 | 1033 | 2 | 0.2 | 1019 | 3 | 0.3 | 0.6433 | 1.52 | ( 0.25, 9.08) | 1.52 | ( 0.25, 9.13) | 0.00 | ( 0.00, 0.01) | |
| >=85 | 986 | 4 | 0.4 | 991 | 3 | 0.3 | 0.7000 | 0.75 | ( 0.17, 3.33) | 0.75 | ( 0.17, 3.34) | 0.00 | (-0.01, 0.00) | |
| History of heart failure | | | | | | | | | | | | | | 0.2087 |
| No | 2970 | 10 | 0.3 | 2979 | 10 | 0.3 | 0.9946 | 1.00 | ( 0.42, 2.39) | 1.00 | ( 0.41, 2.40) | 0.00 | ( 0.00, 0.00) | |
| Yes | 334 | 0 | 0 | 324 | 3 | 0.9 | 0.1248 | 7.22 | ( 0.37,139.14) | 7.28 | ( 0.37,141.55) | 0.01 | ( 0.00, 0.02) | |
| History of renal disease | | | | | | | | | | | | | | |
| Diabetic kidney disease | 1025 | 3 | 0.3 | 1032 | 4 | 0.4 | | | | | | | | |
| Glomerular disease | 816 | 2 | 0.2 | 853 | 2 | 0.2 | | | | | | | | |
| Hypertensive/renovascular disease | 739 | 1 | 0.1 | 706 | 2 | 0.3 | | | | | | | | |
| Other/Unknown | 725 | 4 | 0.6 | 713 | 5 | 0.7 | | | | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6274 |
| <30 | 1151 | 2 | 0.2 | 1131 | 5 | 0.4 | 0.2465 | 2.54 | ( 0.49, 13.09) | 2.55 | ( 0.49, 13.18) | 0.00 | ( 0.00, 0.01) | |
| 30 to <45 | 1461 | 7 | 0.5 | 1467 | 7 | 0.5 | 0.9939 | 1.00 | ( 0.35, 2.83) | 1.00 | ( 0.35, 2.85) | 0.00 | (-0.01, 0.00) | |
| >=45 | 693 | 1 | 0.1 | 706 | 1 | 0.1 | 0.9895 | 0.98 | ( 0.06, 15.66) | 0.98 | ( 0.06, 15.72) | 0.00 | ( 0.00, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8083 |
| Normal (<30) | 663 | 1 | 0.2 | 665 | 2 | 0.3 | 0.5650 | 1.99 | ( 0.18, 21.94) | 2.00 | ( 0.18, 22.08) | 0.00 | ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 6 | 0.6 | 927 | 6 | 0.6 | 0.9851 | 1.01 | ( 0.33, 3.12) | 1.01 | ( 0.32, 3.15) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 3 | 0.2 | 1712 | 5 | 0.3 | 0.4826 | 1.66 | ( 0.40, 6.93) | 1.66 | ( 0.40, 6.96) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8406 |
| Low, moderate or high | 833 | 1 | 0.1 | 839 | 1 | 0.1 | 0.9959 | 0.99 | ( 0.06, 15.85) | 0.99 | ( 0.06, 15.90) | 0.00 | ( 0.00, 0.00) | |
| Very high | 2472 | 9 | 0.4 | 2465 | 12 | 0.5 | 0.5076 | 1.34 | ( 0.56, 3.17) | 1.34 | ( 0.56, 3.18) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.1976 |
| No | 508 | 0 | 0 | 473 | 3 | 0.6 | 0.1152 | 7.52 | ( 0.39,145.14) | 7.57 | ( 0.39,146.85) | 0.01 | ( 0.00, 0.01) | |
| Yes | 2797 | 10 | 0.4 | 2831 | 10 | 0.4 | 0.9784 | 0.99 | ( 0.41, 2.37) | 0.99 | ( 0.41, 2.38) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5406 |
| No | 1940 | 6 | 0.3 | 1908 | 6 | 0.3 | 0.9770 | 1.02 | ( 0.33, 3.15) | 1.02 | ( 0.33, 3.16) | 0.00 | ( 0.00, 0.00) | |
| Yes | 1365 | 4 | 0.3 | 1396 | 7 | 0.5 | 0.3848 | 1.71 | ( 0.50, 5.83) | 1.71 | ( 0.50, 5.87) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2507 |
| No | 1852 | 6 | 0.3 | 1942 | 5 | 0.3 | 0.7033 | 0.79 | ( 0.24, 2.60) | 0.79 | ( 0.24, 2.61) | 0.00 | ( 0.00, 0.00) | |
| Yes | 1453 | 4 | 0.3 | 1362 | 8 | 0.6 | 0.2041 | 2.13 | ( 0.64, 7.07) | 2.14 | ( 0.64, 7.12) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 58 | 1.8 | 3304 | 62 | 1.9 | 0.7112 | 1.07 | ( 0.75, 1.52) | 1.07 | ( 0.75, 1.54) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0458 |
| Male | 2210 | 27 | 1.2 | 2207 | 40 | 1.8 | 0.1083 | 1.48 | ( 0.91, 2.41) | 1.49 | ( 0.91, 2.44) | 0.01 | ( 0.00, 0.01) | |
| Female | 1095 | 31 | 2.8 | 1097 | 22 | 2.0 | 0.2083 | 0.71 | ( 0.41, 1.22) | 0.70 | ( 0.40, 1.22) | -0.01 | (-0.02, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.1637 |
| <65 | 1501 | 13 | 0.9 | 1501 | 21 | 1.4 | 0.1676 | 1.62 | ( 0.81, 3.21) | 1.62 | ( 0.81, 3.26) | 0.01 | ( 0.00, 0.01) | |
| >=65 | 1804 | 45 | 2.5 | 1803 | 41 | 2.3 | 0.6643 | 0.91 | ( 0.60, 1.38) | 0.91 | ( 0.59, 1.40) | 0.00 | (-0.01, 0.01) | |
| Region | | | | | | | | | | | | | | 0.3622 |
| North America | 873 | 14 | 1.6 | 844 | 7 | 0.8 | 0.1445 | 0.52 | ( 0.21, 1.28) | 0.51 | ( 0.21, 1.28) | -0.01 | (-0.02, 0.00) | |
| Europe | 1304 | 31 | 2.4 | 1344 | 37 | 2.8 | 0.5412 | 1.16 | ( 0.72, 1.85) | 1.16 | ( 0.72, 1.89) | 0.00 | (-0.01, 0.02) | |
| Japan | 308 | 7 | 2.3 | 304 | 9 | 3.0 | 0.5939 | 1.30 | ( 0.49, 3.45) | 1.31 | ( 0.48, 3.57) | 0.01 | (-0.02, 0.03) | |
| Other Asia | 820 | 6 | 0.7 | 812 | 9 | 1.1 | 0.4253 | 1.51 | ( 0.54, 4.24) | 1.52 | ( 0.54, 4.29) | 0.00 | (-0.01, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2901 |
| Diabetic | 1515 | 38 | 2.5 | 1525 | 35 | 2.3 | 0.7011 | 0.92 | ( 0.58, 1.44) | 0.91 | ( 0.57, 1.45) | 0.00 | (-0.01, 0.01) | |
| Non-diabetic | 1790 | 20 | 1.1 | 1779 | 27 | 1.5 | 0.2941 | 1.36 | ( 0.76, 2.41) | 1.36 | ( 0.76, 2.44) | 0.00 | ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4362 |
| <30 | 1961 | 35 | 1.8 | 1955 | 33 | 1.7 | 0.8166 | 0.95 | ( 0.59, 1.52) | 0.94 | ( 0.58, 1.53) | 0.00 | (-0.01, 0.01) | |
| >=30 | 1337 | 23 | 1.7 | 1340 | 29 | 2.2 | 0.4054 | 1.26 | ( 0.73, 2.16) | 1.26 | ( 0.73, 2.20) | 0.00 | (-0.01, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | 0.0184 |
| No | 2401 | 27 | 1.1 | 2443 | 43 | 1.8 | 0.0638 | 1.57 | ( 0.97, 2.52) | 1.58 | ( 0.97, 2.56) | 0.01 | ( 0.00, 0.01) | |
| Yes | 904 | 31 | 3.4 | 861 | 19 | 2.2 | 0.1218 | 0.64 | ( 0.37, 1.13) | 0.64 | ( 0.36, 1.13) | -0.01 | (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1832 |
| <130 | 1208 | 17 | 1.4 | 1190 | 25 | 2.1 | 0.1955 | 1.49 | ( 0.81, 2.75) | 1.50 | ( 0.81, 2.80) | 0.01 | ( 0.00, 0.02) | |
| >=130 | 2097 | 41 | 2.0 | 2114 | 37 | 1.8 | 0.6219 | 0.90 | ( 0.58, 1.39) | 0.89 | ( 0.57, 1.40) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.4251 |
| <75 | 1286 | 30 | 2.3 | 1294 | 27 | 2.1 | 0.6705 | 0.89 | ( 0.53, | 1.50) | 0.89 | ( 0.53, | 1.51) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1033 | 17 | 1.6 | 1019 | 17 | 1.7 | 0.9680 | 1.01 | ( 0.52, | 1.97) | 1.01 | ( 0.51, | 2.00) | 0.00 | (-0.01, 0.01) | |
| >=85 | 986 | 11 | 1.1 | 991 | 18 | 1.8 | 0.1950 | 1.63 | ( 0.77, | 3.43) | 1.64 | ( 0.77, | 3.49) | 0.01 | ( 0.00, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | | | 0.5858 |
| No | 2970 | 53 | 1.8 | 2979 | 55 | 1.8 | 0.8584 | 1.03 | ( 0.71, | 1.50) | 1.04 | ( 0.71, | 1.51) | 0.00 | (-0.01, 0.01) | |
| Yes | 334 | 5 | 1.5 | 324 | 7 | 2.2 | 0.5248 | 1.44 | ( 0.46, | 4.50) | 1.45 | ( 0.46, | 4.63) | 0.01 | (-0.01, 0.03) | |
| History of renal disease | | | | | | | | | | | | | | | | 0.3268 |
| Diabetic kidney disease | 1025 | 21 | 2.0 | 1032 | 24 | 2.3 | 0.6678 | 1.14 | ( 0.64, | 2.03) | 1.14 | ( 0.63, | 2.06) | 0.00 | (-0.01, 0.02) | |
| Glomerular disease | 816 | 7 | 0.9 | 853 | 11 | 1.3 | 0.3933 | 1.50 | ( 0.59, | 3.86) | 1.51 | ( 0.58, | 3.91) | 0.00 | (-0.01, 0.01) | |
| Hypertensive/renovascular disease | 739 | 21 | 2.8 | 706 | 13 | 1.8 | 0.2098 | 0.65 | ( 0.33, | 1.28) | 0.64 | ( 0.32, | 1.29) | -0.01 | (-0.03, 0.01) | |
| Other/Unknown | 725 | 9 | 1.2 | 713 | 14 | 2.0 | 0.2751 | 1.58 | ( 0.69, | 3.63) | 1.59 | ( 0.69, | 3.71) | 0.01 | (-0.01, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.3209 |
| <30 | 1151 | 27 | 2.3 | 1131 | 23 | 2.0 | 0.6105 | 0.87 | ( 0.50, | 1.50) | 0.86 | ( 0.49, | 1.52) | 0.00 | (-0.02, 0.01) | |
| 30 to <45 | 1461 | 26 | 1.8 | 1467 | 28 | 1.9 | 0.7952 | 1.07 | ( 0.63, | 1.82) | 1.07 | ( 0.63, | 1.84) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 5 | 0.7 | 706 | 11 | 1.6 | 0.1412 | 2.16 | ( 0.75, | 6.18) | 2.18 | ( 0.75, | 6.30) | 0.01 | ( 0.00, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.2080 |
| Normal (<30) | 663 | 20 | 3.0 | 665 | 15 | 2.3 | 0.3867 | 0.75 | ( 0.39, | 1.45) | 0.74 | ( 0.38, | 1.46) | -0.01 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 16 | 1.7 | 927 | 26 | 2.8 | 0.1105 | 1.64 | ( 0.89, | 3.04) | 1.66 | ( 0.89, | 3.12) | 0.01 | ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 1705 | 22 | 1.3 | 1712 | 21 | 1.2 | 0.8674 | 0.95 | ( 0.52, | 1.72) | 0.95 | ( 0.52, | 1.73) | 0.00 | (-0.01, 0.01) | |

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^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.5082 |
| Low, moderate or high | 833 | 16 | 1.9 | 839 | 14 | 1.7 | 0.6978 | 0.87 | ( 0.43, | 1.77) | 0.87 | ( 0.42, | 1.79) | 0.00 | (-0.02, 0.01) | |
| Very high | 2472 | 42 | 1.7 | 2465 | 48 | 1.9 | 0.5145 | 1.15 | ( 0.76, | 1.73) | 1.15 | ( 0.76, | 1.75) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | | 0.3575 |
| No | 508 | 10 | 2.0 | 473 | 14 | 3.0 | 0.3152 | 1.50 | ( 0.67, | 3.35) | 1.52 | ( 0.67, | 3.45) | 0.01 | (-0.01, 0.03) | |
| Yes | 2797 | 48 | 1.7 | 2831 | 48 | 1.7 | 0.9524 | 0.99 | ( 0.66, | 1.47) | 0.99 | ( 0.66, | 1.48) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.1739 |
| No | 1940 | 29 | 1.5 | 1908 | 38 | 2.0 | 0.2388 | 1.33 | ( 0.83, | 2.15) | 1.34 | ( 0.82, | 2.18) | 0.00 | ( 0.00, 0.01) | |
| Yes | 1365 | 29 | 2.1 | 1396 | 24 | 1.7 | 0.4377 | 0.81 | ( 0.47, | 1.38) | 0.81 | ( 0.47, | 1.39) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.0040 |
| No | 1852 | 16 | 0.9 | 1942 | 35 | 1.8 | 0.0121 | 2.09 | ( 1.16, | 3.76) | 2.11 | ( 1.16, | 3.82) | 0.01 | ( 0.00, 0.02) | |
| Yes | 1453 | 42 | 2.9 | 1362 | 27 | 2.0 | 0.1194 | 0.69 | ( 0.43, | 1.11) | 0.68 | ( 0.42, | 1.11) | -0.01 | (-0.02, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 15 | 0.5 | 3304 | 18 | 0.5 | 0.6000 | 1.20 | ( 0.61, | 2.38) | 1.20 | ( 0.60, | 2.39) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.4810 |
| Male | 2210 | 12 | 0.5 | 2207 | 16 | 0.7 | 0.4461 | 1.34 | ( 0.63, | 2.82) | 1.34 | ( 0.63, | 2.83) | 0.00 | ( 0.00, 0.01) | |
| Female | 1095 | 3 | 0.3 | 1097 | 2 | 0.2 | 0.6529 | 0.67 | ( 0.11, | 3.97) | 0.66 | ( 0.11, | 3.99) | 0.00 | ( 0.00, 0.00) | |
| Age [years] | | | | | | | | | | | | | | | | 0.6048 |
| <65 | 1501 | 3 | 0.2 | 1501 | 5 | 0.3 | 0.4789 | 1.67 | ( 0.40, | 6.96) | 1.67 | ( 0.40, | 7.00) | 0.00 | ( 0.00, 0.01) | |
| >=65 | 1804 | 12 | 0.7 | 1803 | 13 | 0.7 | 0.8398 | 1.08 | ( 0.50, | 2.37) | 1.08 | ( 0.49, | 2.38) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | | | 0.6619 |
| North America | 873 | 4 | 0.5 | 844 | 7 | 0.8 | 0.3352 | 1.81 | ( 0.53, | 6.16) | 1.82 | ( 0.53, | 6.23) | 0.00 | ( 0.00, 0.01) | |
| Europe | 1304 | 10 | 0.8 | 1344 | 10 | 0.7 | 0.9459 | 0.97 | ( 0.41, | 2.32) | 0.97 | ( 0.40, | 2.34) | 0.00 | (-0.01, 0.01) | |
| Japan | 308 | 0 | 0 | 304 | 1 | 0.3 | 0.4731 | 3.04 | ( 0.12, | 74.32) | 3.05 | ( 0.12, | 75.15) | 0.00 | (-0.01, 0.01) | |
| Other Asia | 820 | 1 | 0.1 | 812 | 0 | 0 | 0.4835 | 0.34 | ( 0.01, | 8.25) | 0.34 | ( 0.01, | 8.27) | 0.00 | ( 0.00, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | | 0.0510 |
| Diabetic | 1515 | 11 | 0.7 | 1525 | 7 | 0.5 | 0.3372 | 0.63 | ( 0.25, | 1.63) | 0.63 | ( 0.24, | 1.63) | 0.00 | (-0.01, 0.00) | |
| Non-diabetic | 1790 | 4 | 0.2 | 1779 | 11 | 0.6 | 0.0683 | 2.77 | ( 0.88, | 8.67) | 2.78 | ( 0.88, | 8.74) | 0.00 | ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.7462 |
| <30 | 1961 | 10 | 0.5 | 1955 | 11 | 0.6 | 0.8213 | 1.10 | ( 0.47, | 2.59) | 1.10 | ( 0.47, | 2.61) | 0.00 | ( 0.00, 0.01) | |
| >=30 | 1337 | 5 | 0.4 | 1340 | 7 | 0.5 | 0.5655 | 1.40 | ( 0.44, | 4.39) | 1.40 | ( 0.44, | 4.42) | 0.00 | ( 0.00, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | | | 0.5146 |
| No | 2401 | 9 | 0.4 | 2443 | 13 | 0.5 | 0.4156 | 1.42 | ( 0.61, | 3.31) | 1.42 | ( 0.61, | 3.33) | 0.00 | ( 0.00, 0.01) | |
| Yes | 904 | 6 | 0.7 | 861 | 5 | 0.6 | 0.8247 | 0.87 | ( 0.27, | 2.86) | 0.87 | ( 0.27, | 2.88) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.7169 |
| <130 | 1208 | 5 | 0.4 | 1190 | 7 | 0.6 | 0.5453 | 1.42 | ( 0.45, | 4.47) | 1.42 | ( 0.45, | 4.50) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 2097 | 10 | 0.5 | 2114 | 11 | 0.5 | 0.8413 | 1.09 | ( 0.46, | 2.56) | 1.09 | ( 0.46, | 2.58) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7083 |
| <75 | 1286 | 8 | 0.6 | 1294 | 10 | 0.8 | 0.6456 | 1.24 | ( 0.49, 3.14) | 1.24 | ( 0.49, 3.16) | 0.00 | ( 0.00, 0.01) | |
| 75 to <85 | 1033 | 5 | 0.5 | 1019 | 4 | 0.4 | 0.7539 | 0.81 | ( 0.22, 3.01) | 0.81 | ( 0.22, 3.03) | 0.00 | (-0.01, 0.00) | |
| >=85 | 986 | 2 | 0.2 | 991 | 4 | 0.4 | 0.4171 | 1.99 | ( 0.37, 10.84) | 1.99 | ( 0.36, 10.91) | 0.00 | ( 0.00, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.7639 |
| No | 2970 | 13 | 0.4 | 2979 | 15 | 0.5 | 0.7108 | 1.15 | ( 0.55, 2.41) | 1.15 | ( 0.55, 2.42) | 0.00 | ( 0.00, 0.00) | |
| Yes | 334 | 2 | 0.6 | 324 | 3 | 0.9 | 0.6290 | 1.55 | ( 0.26, 9.19) | 1.55 | ( 0.26, 9.35) | 0.00 | (-0.01, 0.02) | |
| History of renal disease | | | | | | | | | | | | | | 0.4073 |
| Diabetic kidney disease | 1025 | 5 | 0.5 | 1032 | 4 | 0.4 | 0.7306 | 0.79 | ( 0.21, 2.95) | 0.79 | ( 0.21, 2.96) | 0.00 | (-0.01, 0.00) | |
| Glomerular disease | 816 | 0 | 0 | 853 | 4 | 0.5 | 0.0814 | 8.61 | ( 0.46,159.67) | 8.65 | ( 0.47,160.92) | 0.00 | ( 0.00, 0.01) | |
| Hypertensive/renovascular disease | 739 | 6 | 0.8 | 706 | 4 | 0.6 | 0.5739 | 0.70 | ( 0.20, 2.46) | 0.70 | ( 0.20, 2.48) | 0.00 | (-0.01, 0.01) | |
| Other/Unknown | 725 | 4 | 0.6 | 713 | 6 | 0.8 | 0.5085 | 1.53 | ( 0.43, 5.38) | 1.53 | ( 0.43, 5.44) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7501 |
| <30 | 1151 | 7 | 0.6 | 1131 | 10 | 0.9 | 0.4433 | 1.45 | ( 0.56, 3.81) | 1.46 | ( 0.55, 3.84) | 0.00 | ( 0.00, 0.01) | |
| 30 to <45 | 1461 | 6 | 0.4 | 1467 | 5 | 0.3 | 0.7574 | 0.83 | ( 0.25, 2.71) | 0.83 | ( 0.25, 2.72) | 0.00 | (-0.01, 0.00) | |
| >=45 | 693 | 2 | 0.3 | 706 | 3 | 0.4 | 0.6692 | 1.47 | ( 0.25, 8.78) | 1.47 | ( 0.25, 8.85) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9267 |
| Normal (<30) | 663 | 4 | 0.6 | 665 | 4 | 0.6 | 0.9966 | 1.00 | ( 0.25, 3.97) | 1.00 | ( 0.25, 4.00) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 5 | 0.5 | 927 | 7 | 0.8 | 0.5499 | 1.42 | ( 0.45, 4.44) | 1.42 | ( 0.45, 4.48) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 6 | 0.4 | 1712 | 7 | 0.4 | 0.7868 | 1.16 | ( 0.39, 3.45) | 1.16 | ( 0.39, 3.47) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.7982 |
| Low, moderate or high | 833 | 2 | 0.2 | 839 | 3 | 0.4 | 0.6600 | 1.49 | ( 0.25, | 8.89) | 1.49 | ( 0.25, | 8.95) | 0.00 | ( 0.00, 0.01) | |
| Very high | 2472 | 13 | 0.5 | 2465 | 15 | 0.6 | 0.6991 | 1.16 | ( 0.55, | 2.43) | 1.16 | ( 0.55, | 2.44) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | | 0.8768 |
| No | 508 | 3 | 0.6 | 473 | 3 | 0.6 | 0.9301 | 1.07 | ( 0.22, | 5.30) | 1.07 | ( 0.22, | 5.35) | 0.00 | (-0.01, 0.01) | |
| Yes | 2797 | 12 | 0.4 | 2831 | 15 | 0.5 | 0.5842 | 1.23 | ( 0.58, | 2.63) | 1.24 | ( 0.58, | 2.65) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.8047 |
| No | 1940 | 7 | 0.4 | 1908 | 9 | 0.5 | 0.5931 | 1.31 | ( 0.49, | 3.50) | 1.31 | ( 0.49, | 3.52) | 0.00 | ( 0.00, 0.01) | |
| Yes | 1365 | 8 | 0.6 | 1396 | 9 | 0.6 | 0.8439 | 1.10 | ( 0.43, | 2.84) | 1.10 | ( 0.42, | 2.86) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.1348 |
| No | 1852 | 4 | 0.2 | 1942 | 10 | 0.5 | 0.1290 | 2.38 | ( 0.75, | 7.59) | 2.39 | ( 0.75, | 7.64) | 0.00 | ( 0.00, 0.01) | |
| Yes | 1453 | 11 | 0.8 | 1362 | 8 | 0.6 | 0.5827 | 0.78 | ( 0.31, | 1.92) | 0.77 | ( 0.31, | 1.93) | 0.00 | (-0.01, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Symptomatic dehydration (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 24 | 0.7 | 3304 | 30 | 0.9 | 0.4117 | 1.25 | ( 0.73, 2.13) | 1.25 | ( 0.73, 2.15) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.2106 |
| Male | 2210 | 19 | 0.9 | 2207 | 19 | 0.9 | 0.9966 | 1.00 | ( 0.53, 1.89) | 1.00 | ( 0.53, 1.90) | 0.00 | (-0.01, 0.01) | |
| Female | 1095 | 5 | 0.5 | 1097 | 11 | 1.0 | 0.1331 | 2.20 | ( 0.77, 6.30) | 2.21 | ( 0.76, 6.38) | 0.01 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6258 |
| <65 | 1501 | 7 | 0.5 | 1501 | 7 | 0.5 | 1.0000 | 1.00 | ( 0.35, 2.84) | 1.00 | ( 0.35, 2.86) | 0.00 | ( 0.00, 0.00) | |
| >=65 | 1804 | 17 | 0.9 | 1803 | 23 | 1.3 | 0.3392 | 1.35 | ( 0.73, 2.53) | 1.36 | ( 0.72, 2.55) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.7877 |
| North America | 873 | 11 | 1.3 | 844 | 13 | 1.5 | 0.6209 | 1.22 | ( 0.55, 2.71) | 1.23 | ( 0.55, 2.75) | 0.00 | (-0.01, 0.01) | |
| Europe | 1304 | 9 | 0.7 | 1344 | 12 | 0.9 | 0.5566 | 1.29 | ( 0.55, 3.06) | 1.30 | ( 0.54, 3.09) | 0.00 | ( 0.00, 0.01) | |
| Japan | 308 | 3 | 1.0 | 304 | 2 | 0.7 | 0.6640 | 0.68 | ( 0.11, 4.01) | 0.67 | ( 0.11, 4.06) | 0.00 | (-0.02, 0.01) | |
| Other Asia | 820 | 1 | 0.1 | 812 | 3 | 0.4 | 0.3120 | 3.03 | ( 0.32, 29.06) | 3.04 | ( 0.32, 29.26) | 0.00 | ( 0.00, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0247 |
| Diabetic | 1515 | 13 | 0.9 | 1525 | 25 | 1.6 | 0.0526 | 1.91 | ( 0.98, 3.72) | 1.93 | ( 0.98, 3.78) | 0.01 | ( 0.00, 0.02) | |
| Non-diabetic | 1790 | 11 | 0.6 | 1779 | 5 | 0.3 | 0.1360 | 0.46 | ( 0.16, 1.31) | 0.46 | ( 0.16, 1.31) | 0.00 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0018 |
| <30 | 1961 | 17 | 0.9 | 1955 | 8 | 0.4 | 0.0722 | 0.47 | ( 0.20, 1.09) | 0.47 | ( 0.20, 1.09) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1337 | 7 | 0.5 | 1340 | 22 | 1.6 | 0.0052 | 3.14 | ( 1.34, 7.32) | 3.17 | ( 1.35, 7.45) | 0.01 | ( 0.00, 0.02) | |
| Prior CV disease | | | | | | | | | | | | | | 0.7545 |
| No | 2401 | 13 | 0.5 | 2443 | 18 | 0.7 | 0.3939 | 1.36 | ( 0.67, 2.77) | 1.36 | ( 0.67, 2.79) | 0.00 | ( 0.00, 0.01) | |
| Yes | 904 | 11 | 1.2 | 861 | 12 | 1.4 | 0.7432 | 1.15 | ( 0.51, 2.58) | 1.15 | ( 0.50, 2.61) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2042 |
| <130 | 1208 | 8 | 0.7 | 1190 | 15 | 1.3 | 0.1329 | 1.90 | ( 0.81, 4.47) | 1.91 | ( 0.81, 4.53) | 0.01 | ( 0.00, 0.01) | |
| >=130 | 2097 | 16 | 0.8 | 2114 | 15 | 0.7 | 0.8393 | 0.93 | ( 0.46, 1.88) | 0.93 | ( 0.46, 1.88) | 0.00 | (-0.01, 0.00) | |

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User-defined AE category: Symptomatic dehydration (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1941 |
| <75 | 1286 | 10 | 0.8 | 1294 | 20 | 1.5 | 0.0689 | 1.99 | ( 0.93, 4.23) | 2.00 | ( 0.93, 4.30) | 0.01 | ( 0.00, 0.02) | |
| 75 to <85 | 1033 | 6 | 0.6 | 1019 | 4 | 0.4 | 0.5403 | 0.68 | ( 0.19, 2.39) | 0.67 | ( 0.19, 2.40) | 0.00 | (-0.01, 0.00) | |
| >=85 | 986 | 8 | 0.8 | 991 | 6 | 0.6 | 0.5851 | 0.75 | ( 0.26, 2.14) | 0.74 | ( 0.26, 2.15) | 0.00 | (-0.01, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.4635 |
| No | 2970 | 17 | 0.6 | 2979 | 24 | 0.8 | 0.2769 | 1.41 | ( 0.76, 2.61) | 1.41 | ( 0.76, 2.63) | 0.00 | ( 0.00, 0.01) | |
| Yes | 334 | 7 | 2.1 | 324 | 6 | 1.9 | 0.8221 | 0.88 | ( 0.30, 2.60) | 0.88 | ( 0.29, 2.65) | 0.00 | (-0.02, 0.02) | |
| History of renal disease | | | | | | | | | | | | | | 0.0949 |
| Diabetic kidney disease | 1025 | 8 | 0.8 | 1032 | 16 | 1.6 | 0.1040 | 1.99 | ( 0.85, 4.62) | 2.00 | ( 0.85, 4.70) | 0.01 | ( 0.00, 0.02) | |
| Glomerular disease | 816 | 4 | 0.5 | 853 | 1 | 0.1 | 0.1634 | 0.24 | ( 0.03, 2.14) | 0.24 | ( 0.03, 2.14) | 0.00 | (-0.01, 0.00) | |
| Hypertensive/renovascular disease | 739 | 6 | 0.8 | 706 | 2 | 0.3 | 0.1758 | 0.35 | ( 0.07, 1.72) | 0.35 | ( 0.07, 1.73) | -0.01 | (-0.01, 0.00) | |
| Other/Unknown | 725 | 6 | 0.8 | 713 | 11 | 1.5 | 0.2096 | 1.86 | ( 0.69, 5.01) | 1.88 | ( 0.69, 5.10) | 0.01 | ( 0.00, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9277 |
| <30 | 1151 | 11 | 1.0 | 1131 | 15 | 1.3 | 0.4043 | 1.39 | ( 0.64, 3.01) | 1.39 | ( 0.64, 3.05) | 0.00 | (-0.01, 0.01) | |
| 30 to <45 | 1461 | 11 | 0.8 | 1467 | 13 | 0.9 | 0.6893 | 1.18 | ( 0.53, 2.62) | 1.18 | ( 0.53, 2.64) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 2 | 0.3 | 706 | 2 | 0.3 | 0.9852 | 0.98 | ( 0.14, 6.95) | 0.98 | ( 0.14, 6.99) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2601 |
| Normal (<30) | 663 | 5 | 0.8 | 665 | 8 | 1.2 | 0.4061 | 1.60 | ( 0.52, 4.85) | 1.60 | ( 0.52, 4.92) | 0.00 | (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 5 | 0.5 | 927 | 11 | 1.2 | 0.1265 | 2.22 | ( 0.78, 6.38) | 2.24 | ( 0.77, 6.47) | 0.01 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 14 | 0.8 | 1712 | 11 | 0.6 | 0.5402 | 0.78 | ( 0.36, 1.72) | 0.78 | ( 0.35, 1.73) | 0.00 | (-0.01, 0.00) | |

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^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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User-defined AE category: Symptomatic dehydration (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.3204 |
| Low, moderate or high | 833 | 3 | 0.4 | 839 | 7 | 0.8 | 0.2086 | 2.32 | ( 0.60, | 8.93) | 2.33 | ( 0.60, | 9.03) | 0.00 | ( 0.00, 0.01) | |
| Very high | 2472 | 21 | 0.8 | 2465 | 23 | 0.9 | 0.7548 | 1.10 | ( 0.61, | 1.98) | 1.10 | ( 0.61, | 1.99) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | | 0.0561 |
| No | 508 | 8 | 1.6 | 473 | 3 | 0.6 | 0.1621 | 0.40 | ( 0.11, | 1.51) | 0.40 | ( 0.11, | 1.51) | -0.01 | (-0.02, 0.00) | |
| Yes | 2797 | 16 | 0.6 | 2831 | 27 | 1.0 | 0.1001 | 1.67 | ( 0.90, | 3.09) | 1.67 | ( 0.90, | 3.11) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.2749 |
| No | 1940 | 10 | 0.5 | 1908 | 8 | 0.4 | 0.6620 | 0.81 | ( 0.32, | 2.06) | 0.81 | ( 0.32, | 2.06) | 0.00 | (-0.01, 0.00) | |
| Yes | 1365 | 14 | 1.0 | 1396 | 22 | 1.6 | 0.2025 | 1.54 | ( 0.79, | 2.99) | 1.55 | ( 0.79, | 3.03) | 0.01 | ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.6497 |
| No | 1852 | 8 | 0.4 | 1942 | 9 | 0.5 | 0.8846 | 1.07 | ( 0.41, | 2.77) | 1.07 | ( 0.41, | 2.79) | 0.00 | ( 0.00, 0.00) | |
| Yes | 1453 | 16 | 1.1 | 1362 | 21 | 1.5 | 0.3049 | 1.40 | ( 0.73, | 2.67) | 1.41 | ( 0.73, | 2.71) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 50 | 1.5 | 3304 | 52 | 1.6 | 0.8406 | 1.04 | ( 0.71, 1.53) | 1.04 | ( 0.70, 1.54) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0918 |
| Male | 2210 | 41 | 1.9 | 2207 | 35 | 1.6 | 0.4913 | 0.85 | ( 0.55, 1.34) | 0.85 | ( 0.54, 1.34) | 0.00 | (-0.01, 0.00) | |
| Female | 1095 | 9 | 0.8 | 1097 | 17 | 1.5 | 0.1156 | 1.89 | ( 0.84, 4.21) | 1.90 | ( 0.84, 4.28) | 0.01 | ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.5256 |
| <65 | 1501 | 9 | 0.6 | 1501 | 12 | 0.8 | 0.5112 | 1.33 | ( 0.56, 3.15) | 1.34 | ( 0.56, 3.18) | 0.00 | ( 0.00, 0.01) | |
| >=65 | 1804 | 41 | 2.3 | 1803 | 40 | 2.2 | 0.9125 | 0.98 | ( 0.63, 1.50) | 0.98 | ( 0.63, 1.52) | 0.00 | (-0.01, 0.01) | |
| Region | | | | | | | | | | | | | | 0.9768 |
| North America | 873 | 19 | 2.2 | 844 | 19 | 2.3 | 0.9161 | 1.03 | ( 0.55, 1.94) | 1.04 | ( 0.54, 1.97) | 0.00 | (-0.01, 0.01) | |
| Europe | 1304 | 24 | 1.8 | 1344 | 27 | 2.0 | 0.7525 | 1.09 | ( 0.63, 1.88) | 1.09 | ( 0.63, 1.91) | 0.00 | (-0.01, 0.01) | |
| Japan | 308 | 3 | 1.0 | 304 | 3 | 1.0 | 0.9872 | 1.01 | ( 0.21, 4.98) | 1.01 | ( 0.20, 5.06) | 0.00 | (-0.02, 0.02) | |
| Other Asia | 820 | 4 | 0.5 | 812 | 3 | 0.4 | 0.7145 | 0.76 | ( 0.17, 3.37) | 0.76 | ( 0.17, 3.39) | 0.00 | (-0.01, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0763 |
| Diabetic | 1515 | 28 | 1.8 | 1525 | 38 | 2.5 | 0.2234 | 1.35 | ( 0.83, 2.19) | 1.36 | ( 0.83, 2.22) | 0.01 | ( 0.00, 0.02) | |
| Non-diabetic | 1790 | 22 | 1.2 | 1779 | 14 | 0.8 | 0.1863 | 0.64 | ( 0.33, 1.25) | 0.64 | ( 0.33, 1.25) | 0.00 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0005 |
| <30 | 1961 | 34 | 1.7 | 1955 | 17 | 0.9 | 0.0171 | 0.50 | ( 0.28, 0.89) | 0.50 | ( 0.28, 0.89) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1337 | 16 | 1.2 | 1340 | 35 | 2.6 | 0.0074 | 2.18 | ( 1.21, 3.92) | 2.21 | ( 1.22, 4.02) | 0.01 | ( 0.00, 0.02) | |
| Prior CV disease | | | | | | | | | | | | | | 0.8104 |
| No | 2401 | 23 | 1.0 | 2443 | 26 | 1.1 | 0.7116 | 1.11 | ( 0.64, 1.94) | 1.11 | ( 0.63, 1.95) | 0.00 | ( 0.00, 0.01) | |
| Yes | 904 | 27 | 3.0 | 861 | 26 | 3.0 | 0.9676 | 1.01 | ( 0.59, 1.72) | 1.01 | ( 0.59, 1.75) | 0.00 | (-0.02, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3625 |
| <130 | 1208 | 18 | 1.5 | 1190 | 23 | 1.9 | 0.4031 | 1.30 | ( 0.70, 2.39) | 1.30 | ( 0.70, 2.43) | 0.00 | (-0.01, 0.01) | |
| >=130 | 2097 | 32 | 1.5 | 2114 | 29 | 1.4 | 0.6754 | 0.90 | ( 0.55, 1.48) | 0.90 | ( 0.54, 1.49) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.1797 |
| <75 | 1286 | 24 | 1.9 | 1294 | 34 | 2.6 | 0.1922 | 1.41 | ( 0.84, | 2.36) | 1.42 | ( 0.84, | 2.41) | 0.01 | ( 0.00, 0.02) | |
| 75 to <85 | 1033 | 12 | 1.2 | 1019 | 10 | 1.0 | 0.6917 | 0.84 | ( 0.37, | 1.95) | 0.84 | ( 0.36, | 1.96) | 0.00 | (-0.01, 0.01) | |
| >=85 | 986 | 14 | 1.4 | 991 | 8 | 0.8 | 0.1942 | 0.57 | ( 0.24, | 1.35) | 0.57 | ( 0.24, | 1.35) | -0.01 | (-0.02, 0.00) | |
| History of heart failure | | | | | | | | | | | | | | | | 0.6635 |
| No | 2970 | 39 | 1.3 | 2979 | 39 | 1.3 | 0.9893 | 1.00 | ( 0.64, | 1.55) | 1.00 | ( 0.64, | 1.56) | 0.00 | (-0.01, 0.01) | |
| Yes | 334 | 11 | 3.3 | 324 | 13 | 4.0 | 0.6229 | 1.22 | ( 0.55, | 2.68) | 1.23 | ( 0.54, | 2.78) | 0.01 | (-0.02, 0.04) | |
| History of renal disease | | | | | | | | | | | | | | | | 0.1014 |
| Diabetic kidney disease | 1025 | 18 | 1.8 | 1032 | 24 | 2.3 | 0.3612 | 1.32 | ( 0.72, | 2.43) | 1.33 | ( 0.72, | 2.47) | 0.01 | (-0.01, 0.02) | |
| Glomerular disease | 816 | 9 | 1.1 | 853 | 2 | 0.2 | 0.0284 | 0.21 | ( 0.05, | 0.98) | 0.21 | ( 0.05, | 0.98) | -0.01 | (-0.02, 0.00) | |
| Hypertensive/renovascular disease | 739 | 11 | 1.5 | 706 | 8 | 1.1 | 0.5533 | 0.76 | ( 0.31, | 1.88) | 0.76 | ( 0.30, | 1.90) | 0.00 | (-0.02, 0.01) | |
| Other/Unknown | 725 | 12 | 1.7 | 713 | 18 | 2.5 | 0.2488 | 1.53 | ( 0.74, | 3.14) | 1.54 | ( 0.74, | 3.22) | 0.01 | (-0.01, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.8386 |
| <30 | 1151 | 26 | 2.3 | 1131 | 24 | 2.1 | 0.8233 | 0.94 | ( 0.54, | 1.63) | 0.94 | ( 0.54, | 1.64) | 0.00 | (-0.01, 0.01) | |
| 30 to <45 | 1461 | 20 | 1.4 | 1467 | 24 | 1.6 | 0.5526 | 1.20 | ( 0.66, | 2.15) | 1.20 | ( 0.66, | 2.18) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 4 | 0.6 | 706 | 4 | 0.6 | 0.9790 | 0.98 | ( 0.25, | 3.91) | 0.98 | ( 0.24, | 3.94) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.0760 |
| Normal (<30) | 663 | 9 | 1.4 | 665 | 17 | 2.6 | 0.1149 | 1.88 | ( 0.85, | 4.19) | 1.91 | ( 0.84, | 4.31) | 0.01 | ( 0.00, 0.03) | |
| Microalbuminuria (30 to <=300) | 937 | 13 | 1.4 | 927 | 17 | 1.8 | 0.4437 | 1.32 | ( 0.65, | 2.71) | 1.33 | ( 0.64, | 2.75) | 0.00 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 1705 | 28 | 1.6 | 1712 | 18 | 1.1 | 0.1340 | 0.64 | ( 0.36, | 1.15) | 0.64 | ( 0.35, | 1.15) | -0.01 | (-0.01, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.0748 |
| Low, moderate or high | 833 | 7 | 0.8 | 839 | 15 | 1.8 | 0.0891 | 2.13 | ( 0.87, | 5.19) | 2.15 | ( 0.87, | 5.30) | 0.01 | ( 0.00, 0.02) | |
| Very high | 2472 | 43 | 1.7 | 2465 | 37 | 1.5 | 0.5070 | 0.86 | ( 0.56, | 1.33) | 0.86 | ( 0.55, | 1.34) | 0.00 | (-0.01, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | | 0.1128 |
| No | 508 | 15 | 3.0 | 473 | 8 | 1.7 | 0.1920 | 0.57 | ( 0.25, | 1.34) | 0.57 | ( 0.24, | 1.35) | -0.01 | (-0.03, 0.01) | |
| Yes | 2797 | 35 | 1.3 | 2831 | 44 | 1.6 | 0.3342 | 1.24 | ( 0.80, | 1.93) | 1.25 | ( 0.80, | 1.95) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.4986 |
| No | 1940 | 20 | 1.0 | 1908 | 17 | 0.9 | 0.6565 | 0.86 | ( 0.45, | 1.64) | 0.86 | ( 0.45, | 1.65) | 0.00 | (-0.01, 0.00) | |
| Yes | 1365 | 30 | 2.2 | 1396 | 35 | 2.5 | 0.5919 | 1.14 | ( 0.70, | 1.85) | 1.14 | ( 0.70, | 1.87) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.5463 |
| No | 1852 | 15 | 0.8 | 1942 | 14 | 0.7 | 0.7530 | 0.89 | ( 0.43, | 1.84) | 0.89 | ( 0.43, | 1.85) | 0.00 | (-0.01, 0.00) | |
| Yes | 1453 | 35 | 2.4 | 1362 | 38 | 2.8 | 0.5248 | 1.16 | ( 0.74, | 1.82) | 1.16 | ( 0.73, | 1.85) | 0.00 | (-0.01, 0.02) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 29 | 0.9 | 3304 | 24 | 0.7 | 0.4912 | 0.83 | ( 0.48, | 1.42) | 0.83 | ( 0.48, | 1.42) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.4918 |
| Male | 2210 | 24 | 1.1 | 2207 | 18 | 0.8 | 0.3545 | 0.75 | ( 0.41, | 1.38) | 0.75 | ( 0.41, | 1.38) | 0.00 | (-0.01, 0.00) | |
| Female | 1095 | 5 | 0.5 | 1097 | 6 | 0.5 | 0.7648 | 1.20 | ( 0.37, | 3.91) | 1.20 | ( 0.36, | 3.94) | 0.00 | (-0.01, 0.01) | |
| Age [years] | | | | | | | | | | | | | | | | 0.3043 |
| <65 | 1501 | 4 | 0.3 | 1501 | 6 | 0.4 | 0.5264 | 1.50 | ( 0.42, | 5.30) | 1.50 | ( 0.42, | 5.33) | 0.00 | ( 0.00, 0.01) | |
| >=65 | 1804 | 25 | 1.4 | 1803 | 18 | 1.0 | 0.2837 | 0.72 | ( 0.39, | 1.32) | 0.72 | ( 0.39, | 1.32) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | | | 0.4623 |
| North America | 873 | 11 | 1.3 | 844 | 7 | 0.8 | 0.3811 | 0.66 | ( 0.26, | 1.69) | 0.66 | ( 0.25, | 1.70) | 0.00 | (-0.01, 0.01) | |
| Europe | 1304 | 15 | 1.2 | 1344 | 16 | 1.2 | 0.9235 | 1.03 | ( 0.51, | 2.08) | 1.04 | ( 0.51, | 2.10) | 0.00 | (-0.01, 0.01) | |
| Japan | 308 | 0 | 0 | 304 | 1 | 0.3 | 0.4731 | 3.04 | ( 0.12, | 74.32) | 3.05 | ( 0.12, | 75.15) | 0.00 | (-0.01, 0.01) | |
| Other Asia | 820 | 3 | 0.4 | 812 | 0 | 0 | 0.1357 | 0.14 | (<0.01, | 2.79) | 0.14 | (<0.01, | 2.79) | 0.00 | (-0.01, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | | 0.7904 |
| Diabetic | 1515 | 17 | 1.1 | 1525 | 15 | 1.0 | 0.7083 | 0.88 | ( 0.44, | 1.75) | 0.88 | ( 0.44, | 1.76) | 0.00 | (-0.01, 0.01) | |
| Non-diabetic | 1790 | 12 | 0.7 | 1779 | 9 | 0.5 | 0.5206 | 0.75 | ( 0.32, | 1.79) | 0.75 | ( 0.32, | 1.79) | 0.00 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.0785 |
| <30 | 1961 | 18 | 0.9 | 1955 | 9 | 0.5 | 0.0836 | 0.50 | ( 0.23, | 1.11) | 0.50 | ( 0.22, | 1.11) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1337 | 11 | 0.8 | 1340 | 15 | 1.1 | 0.4339 | 1.36 | ( 0.63, | 2.95) | 1.36 | ( 0.62, | 2.98) | 0.00 | ( 0.00, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | | | 0.6847 |
| No | 2401 | 12 | 0.5 | 2443 | 9 | 0.4 | 0.4865 | 0.74 | ( 0.31, | 1.75) | 0.74 | ( 0.31, | 1.75) | 0.00 | (-0.01, 0.00) | |
| Yes | 904 | 17 | 1.9 | 861 | 15 | 1.7 | 0.8276 | 0.93 | ( 0.47, | 1.84) | 0.93 | ( 0.46, | 1.86) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.9933 |
| <130 | 1208 | 11 | 0.9 | 1190 | 9 | 0.8 | 0.6779 | 0.83 | ( 0.35, | 2.00) | 0.83 | ( 0.34, | 2.01) | 0.00 | (-0.01, 0.01) | |
| >=130 | 2097 | 18 | 0.9 | 2114 | 15 | 0.7 | 0.5840 | 0.83 | ( 0.42, | 1.64) | 0.83 | ( 0.41, | 1.64) | 0.00 | (-0.01, 0.00) | |

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User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | 0.5522 |
| <75 | 1286 | 15 | 1.2 | 1294 | 15 | 1.2 | 0.9864 | 0.99 | ( 0.49, | 2.02) | 0.99 | ( 0.48, 2.04) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1033 | 7 | 0.7 | 1019 | 6 | 0.6 | 0.7998 | 0.87 | ( 0.29, | 2.58) | 0.87 | ( 0.29, 2.59) | 0.00 | (-0.01, 0.01) | |
| >=85 | 986 | 7 | 0.7 | 991 | 3 | 0.3 | 0.2019 | 0.43 | ( 0.11, | 1.64) | 0.42 | ( 0.11, 1.65) | 0.00 | (-0.01, 0.00) | |
| History of heart failure | | | | | | | | | | | | | | | 0.1620 |
| No | 2970 | 24 | 0.8 | 2979 | 16 | 0.5 | 0.2010 | 0.66 | ( 0.35, | 1.25) | 0.66 | ( 0.35, 1.25) | 0.00 | (-0.01, 0.00) | |
| Yes | 334 | 5 | 1.5 | 324 | 8 | 2.5 | 0.3703 | 1.65 | ( 0.55, | 4.99) | 1.67 | ( 0.54, 5.15) | 0.01 | (-0.01, 0.03) | |
| History of renal disease | | | | | | | | | | | | | | | 0.4194 |
| Diabetic kidney disease | 1025 | 12 | 1.2 | 1032 | 9 | 0.9 | 0.5005 | 0.74 | ( 0.32, | 1.76) | 0.74 | ( 0.31, 1.77) | 0.00 | (-0.01, 0.01) | |
| Glomerular disease | 816 | 5 | 0.6 | 853 | 1 | 0.1 | 0.0909 | 0.19 | ( 0.02, | 1.63) | 0.19 | ( 0.02, 1.63) | 0.00 | (-0.01, 0.00) | |
| Hypertensive/renovascular disease | 739 | 6 | 0.8 | 706 | 6 | 0.8 | 0.9367 | 1.05 | ( 0.34, | 3.23) | 1.05 | ( 0.34, 3.26) | 0.00 | (-0.01, 0.01) | |
| Other/Unknown | 725 | 6 | 0.8 | 713 | 8 | 1.1 | 0.5697 | 1.36 | ( 0.47, | 3.89) | 1.36 | ( 0.47, 3.94) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | 0.8169 |
| <30 | 1151 | 16 | 1.4 | 1131 | 11 | 1.0 | 0.3564 | 0.70 | ( 0.33, | 1.50) | 0.70 | ( 0.32, 1.51) | 0.00 | (-0.01, 0.00) | |
| 30 to <45 | 1461 | 11 | 0.8 | 1467 | 11 | 0.7 | 0.9923 | 1.00 | ( 0.43, | 2.29) | 1.00 | ( 0.43, 2.30) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 2 | 0.3 | 706 | 2 | 0.3 | 0.9852 | 0.98 | ( 0.14, | 6.95) | 0.98 | ( 0.14, 6.99) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | 0.1243 |
| Normal (<30) | 663 | 4 | 0.6 | 665 | 9 | 1.4 | 0.1651 | 2.24 | ( 0.69, | 7.25) | 2.26 | ( 0.69, 7.38) | 0.01 | ( 0.00, 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 9 | 1.0 | 927 | 7 | 0.8 | 0.6308 | 0.79 | ( 0.29, | 2.10) | 0.78 | ( 0.29, 2.12) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 16 | 0.9 | 1712 | 8 | 0.5 | 0.0992 | 0.50 | ( 0.21, | 1.16) | 0.50 | ( 0.21, 1.16) | 0.00 | (-0.01, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.1010 |
| Low, moderate or high | 833 | 4 | 0.5 | 839 | 8 | 1.0 | 0.2516 | 1.99 | ( 0.60, | 6.57) | 2.00 | ( 0.60, | 6.65) | 0.00 | ( 0.00, 0.01) | |
| Very high | 2472 | 25 | 1.0 | 2465 | 16 | 0.6 | 0.1608 | 0.64 | ( 0.34, | 1.20) | 0.64 | ( 0.34, | 1.20) | 0.00 | (-0.01, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | | 0.6587 |
| No | 508 | 8 | 1.6 | 473 | 5 | 1.1 | 0.4786 | 0.67 | ( 0.22, | 2.04) | 0.67 | ( 0.22, | 2.06) | -0.01 | (-0.02, 0.01) | |
| Yes | 2797 | 21 | 0.8 | 2831 | 19 | 0.7 | 0.7221 | 0.89 | ( 0.48, | 1.66) | 0.89 | ( 0.48, | 1.66) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.9708 |
| No | 1940 | 11 | 0.6 | 1908 | 9 | 0.5 | 0.6810 | 0.83 | ( 0.35, | 2.00) | 0.83 | ( 0.34, | 2.01) | 0.00 | (-0.01, 0.00) | |
| Yes | 1365 | 18 | 1.3 | 1396 | 15 | 1.1 | 0.5550 | 0.81 | ( 0.41, | 1.61) | 0.81 | ( 0.41, | 1.62) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.8149 |
| No | 1852 | 7 | 0.4 | 1942 | 7 | 0.4 | 0.9291 | 0.95 | ( 0.34, | 2.71) | 0.95 | ( 0.33, | 2.72) | 0.00 | ( 0.00, 0.00) | |
| Yes | 1453 | 22 | 1.5 | 1362 | 17 | 1.2 | 0.5463 | 0.82 | ( 0.44, | 1.55) | 0.82 | ( 0.43, | 1.55) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
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Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 135 | 4.1 | 3304 | 107 | 3.2 | 0.0670 | 0.79 | ( 0.62, | 1.02) | 0.79 | ( 0.61, 1.02) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | | 0.1874 |
| Male | 2210 | 100 | 4.5 | 2207 | 71 | 3.2 | 0.0243 | 0.71 | ( 0.53, | 0.96) | 0.70 | ( 0.51, 0.96) | -0.01 | (-0.02, 0.00) | |
| Female | 1095 | 35 | 3.2 | 1097 | 36 | 3.3 | 0.9102 | 1.03 | ( 0.65, | 1.62) | 1.03 | ( 0.64, 1.65) | 0.00 | (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | | | | | 0.9100 |
| <65 | 1501 | 47 | 3.1 | 1501 | 38 | 2.5 | 0.3220 | 0.81 | ( 0.53, | 1.23) | 0.80 | ( 0.52, 1.24) | -0.01 | (-0.02, 0.01) | |
| >=65 | 1804 | 88 | 4.9 | 1803 | 69 | 3.8 | 0.1219 | 0.78 | ( 0.58, | 1.07) | 0.78 | ( 0.56, 1.07) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | | 0.7577 |
| North America | 873 | 45 | 5.2 | 844 | 37 | 4.4 | 0.4540 | 0.85 | ( 0.56, | 1.30) | 0.84 | ( 0.54, 1.32) | -0.01 | (-0.03, 0.01) | |
| Europe | 1304 | 58 | 4.4 | 1344 | 48 | 3.6 | 0.2501 | 0.80 | ( 0.55, | 1.17) | 0.80 | ( 0.54, 1.18) | -0.01 | (-0.02, 0.01) | |
| Japan | 308 | 4 | 1.3 | 304 | 1 | 0.3 | 0.1827 | 0.25 | ( 0.03, | 2.25) | 0.25 | ( 0.03, 2.26) | -0.01 | (-0.02, 0.00) | |
| Other Asia | 820 | 28 | 3.4 | 812 | 21 | 2.6 | 0.3268 | 0.76 | ( 0.43, | 1.32) | 0.75 | ( 0.42, 1.33) | -0.01 | (-0.02, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | 0.1959 |
| Diabetic | 1515 | 81 | 5.3 | 1525 | 73 | 4.8 | 0.4817 | 0.90 | ( 0.66, | 1.22) | 0.89 | ( 0.64, 1.23) | -0.01 | (-0.02, 0.01) | |
| Non-diabetic | 1790 | 54 | 3.0 | 1779 | 34 | 1.9 | 0.0332 | 0.63 | ( 0.41, | 0.97) | 0.63 | ( 0.41, 0.97) | -0.01 | (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | 0.1246 |
| <30 | 1961 | 65 | 3.3 | 1955 | 41 | 2.1 | 0.0189 | 0.63 | ( 0.43, | 0.93) | 0.62 | ( 0.42, 0.93) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1337 | 70 | 5.2 | 1340 | 66 | 4.9 | 0.7148 | 0.94 | ( 0.68, | 1.31) | 0.94 | ( 0.66, 1.32) | 0.00 | (-0.02, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | | 0.6573 |
| No | 2401 | 76 | 3.2 | 2443 | 59 | 2.4 | 0.1127 | 0.76 | ( 0.55, | 1.07) | 0.76 | ( 0.54, 1.07) | -0.01 | (-0.02, 0.00) | |
| Yes | 904 | 59 | 6.5 | 861 | 48 | 5.6 | 0.4024 | 0.85 | ( 0.59, | 1.24) | 0.85 | ( 0.57, 1.25) | -0.01 | (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | 0.1446 |
| <130 | 1208 | 37 | 3.1 | 1190 | 38 | 3.2 | 0.8545 | 1.04 | ( 0.67, | 1.63) | 1.04 | ( 0.66, 1.65) | 0.00 | (-0.01, 0.02) | |
| >=130 | 2097 | 98 | 4.7 | 2114 | 69 | 3.3 | 0.0191 | 0.70 | ( 0.52, | 0.94) | 0.69 | ( 0.50, 0.94) | -0.01 | (-0.03, 0.00) | |

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Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.4726 |
| <75 | 1286 | 61 | 4.7 | 1294 | 55 | 4.3 | 0.5457 | 0.90 | ( 0.63, | 1.28) | 0.89 | ( 0.61, | 1.29) | 0.00 | (-0.02, 0.01) | |
| 75 to <85 | 1033 | 44 | 4.3 | 1019 | 27 | 2.6 | 0.0461 | 0.62 | ( 0.39, | <1.00) | 0.61 | ( 0.38, | 1.00) | -0.02 | (-0.03, 0.00) | |
| >=85 | 986 | 30 | 3.0 | 991 | 25 | 2.5 | 0.4822 | 0.83 | ( 0.49, | 1.40) | 0.82 | ( 0.48, | 1.41) | -0.01 | (-0.02, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | | | 0.0272 |
| No | 2970 | 113 | 3.8 | 2979 | 78 | 2.6 | 0.0094 | 0.69 | ( 0.52, | 0.91) | 0.68 | ( 0.51, | 0.91) | -0.01 | (-0.02, 0.00) | |
| Yes | 334 | 22 | 6.6 | 324 | 29 | 9.0 | 0.2569 | 1.36 | ( 0.80, | 2.31) | 1.39 | ( 0.78, | 2.48) | 0.02 | (-0.02, 0.06) | |
| History of renal disease | | | | | | | | | | | | | | | | 0.3683 |
| Diabetic kidney disease | 1025 | 61 | 6.0 | 1032 | 49 | 4.7 | 0.2252 | 0.80 | ( 0.55, | 1.15) | 0.79 | ( 0.54, | 1.16) | -0.01 | (-0.03, 0.01) | |
| Glomerular disease | 816 | 20 | 2.5 | 853 | 12 | 1.4 | 0.1200 | 0.57 | ( 0.28, | 1.17) | 0.57 | ( 0.28, | 1.17) | -0.01 | (-0.02, 0.00) | |
| Hypertensive/renovascular disease | 739 | 28 | 3.8 | 706 | 17 | 2.4 | 0.1309 | 0.64 | ( 0.35, | 1.15) | 0.63 | ( 0.34, | 1.16) | -0.01 | (-0.03, 0.00) | |
| Other/Unknown | 725 | 26 | 3.6 | 713 | 29 | 4.1 | 0.6344 | 1.13 | ( 0.67, | 1.91) | 1.14 | ( 0.66, | 1.96) | 0.00 | (-0.02, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.2078 |
| <30 | 1151 | 63 | 5.5 | 1131 | 60 | 5.3 | 0.8586 | 0.97 | ( 0.69, | 1.37) | 0.97 | ( 0.67, | 1.39) | 0.00 | (-0.02, 0.02) | |
| 30 to <45 | 1461 | 57 | 3.9 | 1467 | 40 | 2.7 | 0.0757 | 0.70 | ( 0.47, | 1.04) | 0.69 | ( 0.46, | 1.04) | -0.01 | (-0.02, 0.00) | |
| >=45 | 693 | 15 | 2.2 | 706 | 7 | 1.0 | 0.0779 | 0.46 | ( 0.19, | 1.12) | 0.45 | ( 0.18, | 1.12) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.4615 |
| Normal (<30) | 663 | 17 | 2.6 | 665 | 17 | 2.6 | 0.9929 | 1.00 | ( 0.51, | 1.94) | 1.00 | ( 0.50, | 1.97) | 0.00 | (-0.02, 0.02) | |
| Microalbuminuria (30 to <=300) | 937 | 41 | 4.4 | 927 | 37 | 4.0 | 0.6787 | 0.91 | ( 0.59, | 1.41) | 0.91 | ( 0.58, | 1.43) | 0.00 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 77 | 4.5 | 1712 | 53 | 3.1 | 0.0300 | 0.69 | ( 0.49, | 0.97) | 0.68 | ( 0.47, | 0.96) | -0.01 | (-0.03, 0.00) | |

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Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.4092 |
| Low, moderate or high | 833 | 17 | 2.0 | 839 | 10 | 1.2 | 0.1685 | 0.58 | ( 0.27, | 1.27) | 0.58 | ( 0.26, | 1.27) | -0.01 | (-0.02, 0.00) | |
| Very high | 2472 | 118 | 4.8 | 2465 | 97 | 3.9 | 0.1490 | 0.82 | ( 0.63, | 1.07) | 0.82 | ( 0.62, | 1.08) | -0.01 | (-0.02, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | | 0.4285 |
| No | 508 | 27 | 5.3 | 473 | 16 | 3.4 | 0.1396 | 0.64 | ( 0.35, | 1.17) | 0.62 | ( 0.33, | 1.17) | -0.02 | (-0.04, 0.01) | |
| Yes | 2797 | 108 | 3.9 | 2831 | 91 | 3.2 | 0.1889 | 0.83 | ( 0.63, | 1.09) | 0.83 | ( 0.62, | 1.10) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.4782 |
| No | 1940 | 59 | 3.0 | 1908 | 41 | 2.1 | 0.0819 | 0.71 | ( 0.48, | 1.05) | 0.70 | ( 0.47, | 1.05) | -0.01 | (-0.02, 0.00) | |
| Yes | 1365 | 76 | 5.6 | 1396 | 66 | 4.7 | 0.3178 | 0.85 | ( 0.62, | 1.17) | 0.84 | ( 0.60, | 1.18) | -0.01 | (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.4572 |
| No | 1852 | 47 | 2.5 | 1942 | 45 | 2.3 | 0.6588 | 0.91 | ( 0.61, | 1.37) | 0.91 | ( 0.60, | 1.38) | 0.00 | (-0.01, 0.01) | |
| Yes | 1453 | 88 | 6.1 | 1362 | 62 | 4.6 | 0.0758 | 0.75 | ( 0.55, | 1.03) | 0.74 | ( 0.53, | 1.03) | -0.02 | (-0.03, 0.00) | |

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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 8 | 0.2 | 3304 | 8 | 0.2 | 0.9995 | 1.00 | ( 0.38, 2.66) | 1.00 | ( 0.37, 2.67) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.1352 |
| Male | 2210 | 8 | 0.4 | 2207 | 5 | 0.2 | 0.4061 | 0.63 | ( 0.21, 1.91) | 0.63 | ( 0.20, 1.91) | 0.00 | ( 0.00, 0.00) | |
| Female | 1095 | 0 | 0 | 1097 | 3 | 0.3 | 0.1337 | 6.99 | ( 0.36,135.11) | 7.01 | ( 0.36,135.80) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | |
| <65 | 1501 | 6 | 0.4 | 1501 | 2 | 0.1 | | | | | | | | |
| >=65 | 1804 | 2 | 0.1 | 1803 | 6 | 0.3 | | | | | | | | |
| Region | | | | | | | | | | | | | | |
| North America | 873 | 1 | 0.1 | 844 | 2 | 0.2 | | | | | | | | |
| Europe | 1304 | 3 | 0.2 | 1344 | 5 | 0.4 | | | | | | | | |
| Japan | 308 | 0 | 0 | 304 | 0 | 0 | | | | | | | | |
| Other Asia | 820 | 4 | 0.5 | 812 | 1 | 0.1 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | |
| Diabetic | 1515 | 4 | 0.3 | 1525 | 3 | 0.2 | | | | | | | | |
| Non-diabetic | 1790 | 4 | 0.2 | 1779 | 5 | 0.3 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | |
| <30 | 1961 | 5 | 0.3 | 1955 | 3 | 0.2 | | | | | | | | |
| >=30 | 1337 | 3 | 0.2 | 1340 | 5 | 0.4 | | | | | | | | |
| Prior CV disease | | | | | | | | | | | | | | 0.6335 |
| No | 2401 | 5 | 0.2 | 2443 | 6 | 0.2 | 0.7848 | 1.18 | ( 0.36, 3.86) | 1.18 | ( 0.36, 3.87) | 0.00 | ( 0.00, 0.00) | |
| Yes | 904 | 3 | 0.3 | 861 | 2 | 0.2 | 0.6940 | 0.70 | ( 0.12, 4.18) | 0.70 | ( 0.12, 4.20) | 0.00 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2597 |
| <130 | 1208 | 1 | 0.1 | 1190 | 3 | 0.3 | 0.3097 | 3.05 | ( 0.32, 29.24) | 3.05 | ( 0.32, 29.37) | 0.00 | ( 0.00, 0.00) | |
| >=130 | 2097 | 7 | 0.3 | 2114 | 5 | 0.2 | 0.5537 | 0.71 | ( 0.23, 2.23) | 0.71 | ( 0.22, 2.23) | 0.00 | ( 0.00, 0.00) | |

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User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | |
| <75 | 1286 | 3 | 0.2 | 1294 | 3 | 0.2 | | | | | | | |
| 75 to <85 | 1033 | 2 | 0.2 | 1019 | 1 | 0.1 | | | | | | | |
| >=85 | 986 | 3 | 0.3 | 991 | 4 | 0.4 | | | | | | | |
| History of heart failure | | | | | | | | | | | | | 0.5444 |
| No | 2970 | 6 | 0.2 | 2979 | 7 | 0.2 | 0.7855 | 1.16 | ( 0.39, 3.46) | 1.16 | ( 0.39, 3.47) | 0.00 ( 0.00, 0.00) | |
| Yes | 334 | 2 | 0.6 | 324 | 1 | 0.3 | 0.5807 | 0.52 | ( 0.05, 5.66) | 0.51 | ( 0.05, 5.70) | 0.00 (-0.01, 0.01) | |
| History of renal disease | | | | | | | | | | | | | |
| Diabetic kidney disease | 1025 | 1 | 0.1 | 1032 | 3 | 0.3 | | | | | | | |
| Glomerular disease | 816 | 2 | 0.2 | 853 | 0 | 0 | | | | | | | |
| Hypertensive/renovascular disease | 739 | 3 | 0.4 | 706 | 2 | 0.3 | | | | | | | |
| Other/Unknown | 725 | 2 | 0.3 | 713 | 3 | 0.4 | | | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.7666 |
| <30 | 1151 | 2 | 0.2 | 1131 | 2 | 0.2 | 0.9860 | 1.02 | ( 0.14, 7.21) | 1.02 | ( 0.14, 7.24) | 0.00 ( 0.00, 0.00) | |
| 30 to <45 | 1461 | 6 | 0.4 | 1467 | 5 | 0.3 | 0.7574 | 0.83 | ( 0.25, 2.71) | 0.83 | ( 0.25, 2.72) | 0.00 (-0.01, 0.00) | |
| >=45 | 693 | 0 | 0 | 706 | 1 | 0.1 | 0.4874 | 2.94 | ( 0.12, 72.16) | 2.95 | ( 0.12, 72.51) | 0.00 ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | |
| Normal (<30) | 663 | 3 | 0.5 | 665 | 2 | 0.3 | | | | | | | |
| Microalbuminuria (30 to <=300) | 937 | 1 | 0.1 | 927 | 4 | 0.4 | | | | | | | |
| Macroalbuminuria (>300) | 1705 | 4 | 0.2 | 1712 | 2 | 0.1 | | | | | | | |

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| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | 0.9923 |
| Low, moderate or high | 833 | 3 | 0.4 | 839 | 3 | 0.4 | 0.9930 | 0.99 | ( 0.20, | 4.90) | 0.99 | ( 0.20, 4.93) | 0.00 | (-0.01, 0.01) | |
| Very high | 2472 | 5 | 0.2 | 2465 | 5 | 0.2 | 0.9964 | 1.00 | ( 0.29, | 3.46) | 1.00 | ( 0.29, 3.47) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | 0.5021 |
| No | 508 | 1 | 0.2 | 473 | 0 | 0 | 0.5106 | 0.36 | ( 0.01, | 8.77) | 0.36 | ( 0.01, 8.79) | 0.00 | (-0.01, 0.00) | |
| Yes | 2797 | 7 | 0.3 | 2831 | 8 | 0.3 | 0.8141 | 1.13 | ( 0.41, | 3.11) | 1.13 | ( 0.41, 3.12) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | 0.5667 |
| No | 1940 | 5 | 0.3 | 1908 | 6 | 0.3 | 0.7417 | 1.22 | ( 0.37, | 3.99) | 1.22 | ( 0.37, 4.01) | 0.00 | ( 0.00, 0.00) | |
| Yes | 1365 | 3 | 0.2 | 1396 | 2 | 0.1 | 0.6364 | 0.65 | ( 0.11, | 3.90) | 0.65 | ( 0.11, 3.90) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | |
| No | 1852 | 3 | 0.2 | 1942 | 4 | 0.2 | | | | | | | | | |
| Yes | 1453 | 5 | 0.3 | 1362 | 4 | 0.3 | | | | | | | | | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 109 | 3.3 | 3304 | 92 | 2.8 | 0.2241 | 0.84 | ( 0.64, | 1.11) | 0.84 | ( 0.63, | 1.11) | -0.01 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.5944 |
| Male | 2210 | 77 | 3.5 | 2207 | 68 | 3.1 | 0.4522 | 0.88 | ( 0.64, | 1.22) | 0.88 | ( 0.63, | 1.23) | 0.00 | (-0.01, 0.01) | |
| Female | 1095 | 32 | 2.9 | 1097 | 24 | 2.2 | 0.2758 | 0.75 | ( 0.44, | 1.26) | 0.74 | ( 0.43, | 1.27) | -0.01 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | | | | 0.2881 |
| <65 | 1501 | 47 | 3.1 | 1501 | 33 | 2.2 | 0.1126 | 0.70 | ( 0.45, | 1.09) | 0.70 | ( 0.44, | 1.09) | -0.01 | (-0.02, 0.00) | |
| >=65 | 1804 | 62 | 3.4 | 1803 | 59 | 3.3 | 0.7838 | 0.95 | ( 0.67, | 1.35) | 0.95 | ( 0.66, | 1.37) | 0.00 | (-0.01, 0.01) | |
| Region | | | | | | | | | | | | | | | | 0.9462 |
| North America | 873 | 35 | 4.0 | 844 | 27 | 3.2 | 0.3684 | 0.80 | ( 0.49, | 1.31) | 0.79 | ( 0.47, | 1.32) | -0.01 | (-0.03, 0.01) | |
| Europe | 1304 | 54 | 4.1 | 1344 | 50 | 3.7 | 0.5773 | 0.90 | ( 0.62, | 1.31) | 0.89 | ( 0.60, | 1.32) | 0.00 | (-0.02, 0.01) | |
| Japan | 308 | 2 | 0.6 | 304 | 1 | 0.3 | 0.5704 | 0.51 | ( 0.05, | 5.56) | 0.50 | ( 0.05, | 5.60) | 0.00 | (-0.01, 0.01) | |
| Other Asia | 820 | 18 | 2.2 | 812 | 14 | 1.7 | 0.4926 | 0.79 | ( 0.39, | 1.57) | 0.78 | ( 0.39, | 1.58) | 0.00 | (-0.02, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | | 0.5704 |
| Diabetic | 1515 | 62 | 4.1 | 1525 | 49 | 3.2 | 0.1962 | 0.79 | ( 0.54, | 1.13) | 0.78 | ( 0.53, | 1.14) | -0.01 | (-0.02, 0.00) | |
| Non-diabetic | 1790 | 47 | 2.6 | 1779 | 43 | 2.4 | 0.6910 | 0.92 | ( 0.61, | 1.38) | 0.92 | ( 0.60, | 1.40) | 0.00 | (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.3597 |
| <30 | 1961 | 56 | 2.9 | 1955 | 53 | 2.7 | 0.7832 | 0.95 | ( 0.66, | 1.37) | 0.95 | ( 0.65, | 1.39) | 0.00 | (-0.01, 0.01) | |
| >=30 | 1337 | 53 | 4.0 | 1340 | 39 | 2.9 | 0.1346 | 0.73 | ( 0.49, | 1.10) | 0.73 | ( 0.48, | 1.11) | -0.01 | (-0.02, 0.00) | |
| Prior CV disease | | | | | | | | | | | | | | | | 0.9188 |
| No | 2401 | 76 | 3.2 | 2443 | 66 | 2.7 | 0.3387 | 0.85 | ( 0.62, | 1.18) | 0.85 | ( 0.61, | 1.19) | 0.00 | (-0.01, 0.00) | |
| Yes | 904 | 33 | 3.7 | 861 | 26 | 3.0 | 0.4612 | 0.83 | ( 0.50, | 1.37) | 0.82 | ( 0.49, | 1.39) | -0.01 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.7343 |
| <130 | 1208 | 29 | 2.4 | 1190 | 26 | 2.2 | 0.7241 | 0.91 | ( 0.54, | 1.54) | 0.91 | ( 0.53, | 1.55) | 0.00 | (-0.01, 0.01) | |
| >=130 | 2097 | 80 | 3.8 | 2114 | 66 | 3.1 | 0.2191 | 0.82 | ( 0.59, | 1.13) | 0.81 | ( 0.58, | 1.13) | -0.01 | (-0.02, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.0428 |
| <75 | 1286 | 44 | 3.4 | 1294 | 42 | 3.2 | 0.8037 | 0.95 | ( 0.63, | 1.44) | 0.95 | ( 0.62, | 1.46) | 0.00 | (-0.02, 0.01) | |
| 75 to <85 | 1033 | 41 | 4.0 | 1019 | 20 | 2.0 | 0.0075 | 0.49 | ( 0.29, | 0.84) | 0.48 | ( 0.28, | 0.83) | -0.02 | (-0.03,-0.01) | |
| >=85 | 986 | 24 | 2.4 | 991 | 30 | 3.0 | 0.4185 | 1.24 | ( 0.73, | 2.11) | 1.25 | ( 0.73, | 2.16) | 0.01 | (-0.01, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | | | 0.0790 |
| No | 2970 | 93 | 3.1 | 2979 | 86 | 2.9 | 0.5811 | 0.92 | ( 0.69, | 1.23) | 0.92 | ( 0.68, | 1.24) | 0.00 | (-0.01, 0.01) | |
| Yes | 334 | 16 | 4.8 | 324 | 6 | 1.9 | 0.0361 | 0.39 | ( 0.15, | 0.98) | 0.38 | ( 0.14, | 0.97) | -0.03 | (-0.06, 0.00) | |
| History of renal disease | | | | | | | | | | | | | | | | 0.8591 |
| Diabetic kidney disease | 1025 | 38 | 3.7 | 1032 | 30 | 2.9 | 0.3100 | 0.78 | ( 0.49, | 1.26) | 0.78 | ( 0.48, | 1.27) | -0.01 | (-0.02, 0.01) | |
| Glomerular disease | 816 | 20 | 2.5 | 853 | 15 | 1.8 | 0.3237 | 0.72 | ( 0.37, | 1.39) | 0.71 | ( 0.36, | 1.40) | -0.01 | (-0.02, 0.01) | |
| Hypertensive/renovascular disease | 739 | 25 | 3.4 | 706 | 24 | 3.4 | 0.9862 | 1.00 | ( 0.58, | 1.74) | 1.01 | ( 0.57, | 1.78) | 0.00 | (-0.02, 0.02) | |
| Other/Unknown | 725 | 26 | 3.6 | 713 | 23 | 3.2 | 0.7064 | 0.90 | ( 0.52, | 1.56) | 0.90 | ( 0.51, | 1.59) | 0.00 | (-0.02, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.8932 |
| <30 | 1151 | 65 | 5.6 | 1131 | 53 | 4.7 | 0.2999 | 0.83 | ( 0.58, | 1.18) | 0.82 | ( 0.57, | 1.19) | -0.01 | (-0.03, 0.01) | |
| 30 to <45 | 1461 | 37 | 2.5 | 1467 | 34 | 2.3 | 0.7055 | 0.92 | ( 0.58, | 1.45) | 0.91 | ( 0.57, | 1.46) | 0.00 | (-0.01, 0.01) | |
| >=45 | 693 | 7 | 1.0 | 706 | 5 | 0.7 | 0.5404 | 0.70 | ( 0.22, | 2.20) | 0.70 | ( 0.22, | 2.21) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.9463 |
| Normal (<30) | 663 | 16 | 2.4 | 665 | 14 | 2.1 | 0.7057 | 0.87 | ( 0.43, | 1.77) | 0.87 | ( 0.42, | 1.80) | 0.00 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 31 | 3.3 | 927 | 24 | 2.6 | 0.3588 | 0.78 | ( 0.46, | 1.32) | 0.78 | ( 0.45, | 1.33) | -0.01 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 62 | 3.6 | 1712 | 54 | 3.2 | 0.4365 | 0.87 | ( 0.61, | 1.24) | 0.86 | ( 0.60, | 1.25) | 0.00 | (-0.02, 0.01) | |

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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.9569 |
| Low, moderate or high | 833 | 8 | 1.0 | 839 | 7 | 0.8 | 0.7846 | 0.87 | ( 0.32, | 2.38) | 0.87 | ( 0.31, | 2.40) | 0.00 | (-0.01, 0.01) | |
| Very high | 2472 | 101 | 4.1 | 2465 | 85 | 3.4 | 0.2395 | 0.84 | ( 0.64, | 1.12) | 0.84 | ( 0.62, | 1.13) | -0.01 | (-0.02, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | | 0.2999 |
| No | 508 | 17 | 3.3 | 473 | 9 | 1.9 | 0.1595 | 0.57 | ( 0.26, | 1.26) | 0.56 | ( 0.25, | 1.27) | -0.01 | (-0.03, 0.01) | |
| Yes | 2797 | 92 | 3.3 | 2831 | 83 | 2.9 | 0.4399 | 0.89 | ( 0.67, | 1.19) | 0.89 | ( 0.66, | 1.20) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.7540 |
| No | 1940 | 52 | 2.7 | 1908 | 45 | 2.4 | 0.5242 | 0.88 | ( 0.59, | 1.30) | 0.88 | ( 0.59, | 1.31) | 0.00 | (-0.01, 0.01) | |
| Yes | 1365 | 57 | 4.2 | 1396 | 47 | 3.4 | 0.2643 | 0.81 | ( 0.55, | 1.18) | 0.80 | ( 0.54, | 1.19) | -0.01 | (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.4896 |
| No | 1852 | 65 | 3.5 | 1942 | 53 | 2.7 | 0.1662 | 0.78 | ( 0.54, | 1.11) | 0.77 | ( 0.53, | 1.12) | -0.01 | (-0.02, 0.00) | |
| Yes | 1453 | 44 | 3.0 | 1362 | 39 | 2.9 | 0.7962 | 0.95 | ( 0.62, | 1.45) | 0.94 | ( 0.61, | 1.46) | 0.00 | (-0.01, 0.01) | |

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MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3305 | 19 | 0.6 | 3304 | 16 | 0.5 | 0.6118 | 0.84 | ( 0.43, 1.64) | 0.84 | ( 0.43, 1.64) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.1465 |
| Male | 2210 | 13 | 0.6 | 2207 | 7 | 0.3 | 0.1797 | 0.54 | ( 0.22, 1.35) | 0.54 | ( 0.21, 1.35) | 0.00 | (-0.01, 0.00) | |
| Female | 1095 | 6 | 0.5 | 1097 | 9 | 0.8 | 0.4391 | 1.50 | ( 0.53, 4.19) | 1.50 | ( 0.53, 4.23) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6671 |
| <65 | 1501 | 6 | 0.4 | 1501 | 4 | 0.3 | 0.5264 | 0.67 | ( 0.19, 2.36) | 0.67 | ( 0.19, 2.36) | 0.00 | (-0.01, 0.00) | |
| >=65 | 1804 | 13 | 0.7 | 1803 | 12 | 0.7 | 0.8420 | 0.92 | ( 0.42, 2.02) | 0.92 | ( 0.42, 2.03) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.8765 |
| North America | 873 | 10 | 1.1 | 844 | 6 | 0.7 | 0.3488 | 0.62 | ( 0.23, 1.70) | 0.62 | ( 0.22, 1.71) | 0.00 | (-0.01, 0.00) | |
| Europe | 1304 | 6 | 0.5 | 1344 | 7 | 0.5 | 0.8232 | 1.13 | ( 0.38, 3.36) | 1.13 | ( 0.38, 3.38) | 0.00 | ( 0.00, 0.01) | |
| Japan | 308 | 1 | 0.3 | 304 | 1 | 0.3 | 0.9926 | 1.01 | ( 0.06, 16.12) | 1.01 | ( 0.06, 16.27) | 0.00 | (-0.01, 0.01) | |
| Other Asia | 820 | 2 | 0.2 | 812 | 2 | 0.2 | 0.9922 | 1.01 | ( 0.14, 7.15) | 1.01 | ( 0.14, 7.19) | 0.00 | ( 0.00, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4192 |
| Diabetic | 1515 | 19 | 1.3 | 1525 | 15 | 1.0 | 0.4782 | 0.78 | ( 0.40, 1.54) | 0.78 | ( 0.40, 1.55) | 0.00 | (-0.01, 0.00) | |
| Non-diabetic | 1790 | 0 | 0 | 1779 | 1 | 0.1 | 0.4767 | 3.02 | ( 0.12, 74.05) | 3.02 | ( 0.12, 74.19) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6864 |
| <30 | 1961 | 8 | 0.4 | 1955 | 6 | 0.3 | 0.5963 | 0.75 | ( 0.26, 2.16) | 0.75 | ( 0.26, 2.17) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1337 | 10 | 0.7 | 1340 | 10 | 0.7 | 0.9960 | 1.00 | ( 0.42, 2.39) | 1.00 | ( 0.41, 2.41) | 0.00 | (-0.01, 0.01) | |
| Prior CV disease | | | | | | | | | | | | | | 0.4246 |
| No | 2401 | 9 | 0.4 | 2443 | 10 | 0.4 | 0.8477 | 1.09 | ( 0.44, 2.68) | 1.09 | ( 0.44, 2.69) | 0.00 | ( 0.00, 0.00) | |
| Yes | 904 | 10 | 1.1 | 861 | 6 | 0.7 | 0.3644 | 0.63 | ( 0.23, 1.73) | 0.63 | ( 0.23, 1.73) | 0.00 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0073 |
| <130 | 1208 | 2 | 0.2 | 1190 | 9 | 0.8 | 0.0323 | 4.57 | ( 0.99, 21.10) | 4.60 | ( 0.99, 21.31) | 0.01 | ( 0.00, 0.01) | |
| >=130 | 2097 | 17 | 0.8 | 2114 | 7 | 0.3 | 0.0387 | 0.41 | ( 0.17, 0.98) | 0.41 | ( 0.17, 0.98) | 0.00 | (-0.01, 0.00) | |

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^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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User-defined AE category: Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5162 |
| <75 | 1286 | 10 | 0.8 | 1294 | 10 | 0.8 | 0.9889 | 0.99 | ( 0.42, 2.38) | 0.99 | ( 0.41, 2.40) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1033 | 8 | 0.8 | 1019 | 4 | 0.4 | 0.2566 | 0.51 | ( 0.15, 1.68) | 0.50 | ( 0.15, 1.68) | 0.00 | (-0.01, 0.00) | |
| >=85 | 986 | 1 | 0.1 | 991 | 2 | 0.2 | 0.5664 | 1.99 | ( 0.18, 21.91) | 1.99 | ( 0.18, 22.00) | 0.00 | ( 0.00, 0.00) | |
| History of heart failure | | | | | | | | | | | | | | 0.8958 |
| No | 2970 | 15 | 0.5 | 2979 | 13 | 0.4 | 0.6988 | 0.86 | ( 0.41, 1.81) | 0.86 | ( 0.41, 1.82) | 0.00 | ( 0.00, 0.00) | |
| Yes | 334 | 4 | 1.2 | 324 | 3 | 0.9 | 0.7342 | 0.77 | ( 0.17, 3.43) | 0.77 | ( 0.17, 3.47) | 0.00 | (-0.02, 0.01) | |
| History of renal disease | | | | | | | | | | | | | | 0.8568 |
| Diabetic kidney disease | 1025 | 17 | 1.7 | 1032 | 13 | 1.3 | 0.4506 | 0.76 | ( 0.37, 1.56) | 0.76 | ( 0.37, 1.57) | 0.00 | (-0.01, 0.01) | |
| Glomerular disease | 816 | 0 | 0 | 853 | 0 | 0 | 0.9823 | 0.96 | ( 0.02, 48.16) | 0.96 | ( 0.02, 48.27) | 0.00 | ( 0.00, 0.00) | |
| Hypertensive/renovascular disease | 739 | 0 | 0 | 706 | 1 | 0.1 | 0.4593 | 3.14 | ( 0.13, 76.95) | 3.14 | ( 0.13, 77.32) | 0.00 | ( 0.00, 0.01) | |
| Other/Unknown | 725 | 2 | 0.3 | 713 | 2 | 0.3 | 0.9867 | 1.02 | ( 0.14, 7.20) | 1.02 | ( 0.14, 7.24) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9787 |
| <30 | 1151 | 9 | 0.8 | 1131 | 7 | 0.6 | 0.6408 | 0.79 | ( 0.30, 2.12) | 0.79 | ( 0.29, 2.13) | 0.00 | (-0.01, 0.01) | |
| 30 to <45 | 1461 | 8 | 0.5 | 1467 | 7 | 0.5 | 0.7896 | 0.87 | ( 0.32, 2.40) | 0.87 | ( 0.31, 2.41) | 0.00 | (-0.01, 0.00) | |
| >=45 | 693 | 2 | 0.3 | 706 | 2 | 0.3 | 0.9852 | 0.98 | ( 0.14, 6.95) | 0.98 | ( 0.14, 6.99) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8139 |
| Normal (<30) | 663 | 3 | 0.5 | 665 | 3 | 0.5 | 0.9970 | 1.00 | ( 0.20, 4.92) | 1.00 | ( 0.20, 4.96) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 8 | 0.9 | 927 | 5 | 0.5 | 0.4147 | 0.63 | ( 0.21, 1.92) | 0.63 | ( 0.21, 1.93) | 0.00 | (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 1705 | 8 | 0.5 | 1712 | 8 | 0.5 | 0.9934 | 1.00 | ( 0.37, 2.65) | 1.00 | ( 0.37, 2.66) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the final follow-up visit, overall and by subgroup - TS
User-defined AE category: Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.8623 |
| Low, moderate or high | 833 | 2 | 0.2 | 839 | 2 | 0.2 | 0.9943 | 0.99 | ( 0.14, | 7.03) | 0.99 | ( 0.14, | 7.06) | 0.00 | ( 0.00, 0.00) | |
| Very high | 2472 | 17 | 0.7 | 2465 | 14 | 0.6 | 0.5943 | 0.83 | ( 0.41, | 1.67) | 0.82 | ( 0.41, | 1.68) | 0.00 | (-0.01, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | | 0.4389 |
| No | 508 | 3 | 0.6 | 473 | 4 | 0.8 | 0.6352 | 1.43 | ( 0.32, | 6.36) | 1.44 | ( 0.32, | 6.45) | 0.00 | (-0.01, 0.01) | |
| Yes | 2797 | 16 | 0.6 | 2831 | 12 | 0.4 | 0.4296 | 0.74 | ( 0.35, | 1.56) | 0.74 | ( 0.35, | 1.57) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.3622 |
| No | 1940 | 9 | 0.5 | 1908 | 5 | 0.3 | 0.2984 | 0.56 | ( 0.19, | 1.68) | 0.56 | ( 0.19, | 1.69) | 0.00 | (-0.01, 0.00) | |
| Yes | 1365 | 10 | 0.7 | 1396 | 11 | 0.8 | 0.8670 | 1.08 | ( 0.46, | 2.52) | 1.08 | ( 0.46, | 2.54) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.8155 |
| No | 1852 | 5 | 0.3 | 1942 | 4 | 0.2 | 0.6854 | 0.76 | ( 0.21, | 2.84) | 0.76 | ( 0.20, | 2.84) | 0.00 | ( 0.00, 0.00) | |
| Yes | 1453 | 14 | 1.0 | 1362 | 12 | 0.9 | 0.8192 | 0.91 | ( 0.42, | 1.97) | 0.91 | ( 0.42, | 1.98) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.137. $Only severe events are included. ***Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
^Events confirmed or unrefuted by adjudication are considered as an endpoint event.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.1.2.4**

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 473 | 14.3 | 3304 | 431 | 13.0 | 0.1340 | 0.91 (0.81, 1.03) | 0.90 (0.78, 1.03) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** | |
| Overall | 3305 | 359 | 10.9 | 3304 | 378 | 11.4 | 0.4552 | 1.05 (0.92, 1.21) | 1.06 (0.91, 1.24) | 0.01 (-0.01, 0.02) | | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Surgical and medical procedures

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 307 | 9.3 | 3304 | 257 | 7.8 | 0.0280 | 0.84 (0.71, 0.98) | 0.82 (0.69, 0.98) | -0.02 (-0.03, 0.00) | |
| Sex | | | | | | | | | | | 0.1302 |
| Male | 2210 | 205 | 9.3 | 2207 | 186 | 8.4 | 0.3210 | 0.91 (0.75, 1.10) | 0.90 (0.73, 1.11) | -0.01 (-0.03, 0.01) | |
| Female | 1095 | 102 | 9.3 | 1097 | 71 | 6.5 | 0.0136 | 0.69 (0.52, 0.93) | 0.67 (0.49, 0.92) | -0.03 (-0.05,-0.01) | |
| Age [years] | | | | | | | | | | | 0.6794 |
| <65 | 1501 | 110 | 7.3 | 1501 | 88 | 5.9 | 0.1057 | 0.80 (0.61, 1.05) | 0.79 (0.59, 1.05) | -0.01 (-0.03, 0.00) | |
| >=65 | 1804 | 197 | 10.9 | 1803 | 169 | 9.4 | 0.1239 | 0.86 (0.71, 1.04) | 0.84 (0.68, 1.05) | -0.02 (-0.04, 0.00) | |
| Region | | | | | | | | | | | 0.6363 |
| North America | 873 | 54 | 6.2 | 844 | 52 | 6.2 | 0.9832 | 1.00 (0.69, 1.44) | 1.00 (0.67, 1.48) | 0.00 (-0.02, 0.02) | |
| Europe | 1304 | 161 | 12.3 | 1344 | 137 | 10.2 | 0.0796 | 0.83 (0.67, 1.02) | 0.81 (0.63, 1.03) | -0.02 (-0.05, 0.00) | |
| Japan | 308 | 51 | 16.6 | 304 | 35 | 11.5 | 0.0725 | 0.70 (0.47, 1.04) | 0.66 (0.41, 1.04) | -0.05 (-0.11, 0.00) | |
| Other Asia | 820 | 41 | 5.0 | 812 | 33 | 4.1 | 0.3635 | 0.81 (0.52, 1.27) | 0.80 (0.50, 1.29) | -0.01 (-0.03, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.5964 |
| Diabetic | 1515 | 174 | 11.5 | 1525 | 141 | 9.2 | 0.0428 | 0.81 (0.65, 0.99) | 0.79 (0.62, 0.99) | -0.02 (-0.04, 0.00) | |
| Non-diabetic | 1790 | 133 | 7.4 | 1779 | 116 | 6.5 | 0.2862 | 0.88 (0.69, 1.12) | 0.87 (0.67, 1.12) | -0.01 (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.4862 |
| <30 | 1961 | 184 | 9.4 | 1955 | 147 | 7.5 | 0.0360 | 0.80 (0.65, 0.99) | 0.79 (0.63, 0.98) | -0.02 (-0.04, 0.00) | |
| >=30 | 1337 | 121 | 9.1 | 1340 | 109 | 8.1 | 0.3979 | 0.90 (0.70, 1.15) | 0.89 (0.68, 1.17) | -0.01 (-0.03, 0.01) | |
| Prior CV disease | | | | | | | | | | | 0.5457 |
| No | 2401 | 179 | 7.5 | 2443 | 160 | 6.5 | 0.2166 | 0.88 (0.72, 1.08) | 0.87 (0.70, 1.09) | -0.01 (-0.02, 0.01) | |
| Yes | 904 | 128 | 14.2 | 861 | 97 | 11.3 | 0.0685 | 0.80 (0.62, 1.02) | 0.77 (0.58, 1.02) | -0.03 (-0.06, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.5307 |
| <130 | 1208 | 113 | 9.4 | 1190 | 87 | 7.3 | 0.0704 | 0.78 (0.60, 1.02) | 0.76 (0.57, 1.02) | -0.02 (-0.04, 0.00) | |
| >=130 | 2097 | 194 | 9.3 | 2114 | 170 | 8.0 | 0.1625 | 0.87 (0.71, 1.06) | 0.86 (0.69, 1.06) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Surgical and medical procedures

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6075 |
| <75 | 1286 | 151 | 11.7 | 1294 | 117 | 9.0 | 0.0246 | 0.77 | (0.61, 0.97) | 0.75 | (0.58, 0.96) | -0.03 | (-0.05, 0.00) | |
| 75 to <85 | 1033 | 85 | 8.2 | 1019 | 74 | 7.3 | 0.4130 | 0.88 | (0.65, 1.19) | 0.87 | (0.63, 1.21) | -0.01 | (-0.03, 0.01) | |
| >=85 | 986 | 71 | 7.2 | 991 | 66 | 6.7 | 0.6359 | 0.92 | (0.67, 1.28) | 0.92 | (0.65, 1.30) | -0.01 | (-0.03, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.6159 |
| No | 2970 | 247 | 8.3 | 2979 | 212 | 7.1 | 0.0829 | 0.86 | (0.72, 1.02) | 0.84 | (0.70, 1.02) | -0.01 | (-0.03, 0.00) | |
| Yes | 334 | 60 | 18.0 | 324 | 45 | 13.9 | 0.1536 | 0.77 | (0.54, 1.10) | 0.74 | (0.48, 1.12) | -0.04 | (-0.10, 0.02) | |
| History of renal disease | | | | | | | | | | | | | | 0.2585 |
| Diabetic kidney disease | 1025 | 105 | 10.2 | 1032 | 90 | 8.7 | 0.2384 | 0.85 | (0.65, 1.11) | 0.84 | (0.62, 1.13) | -0.02 | (-0.04, 0.01) | |
| Glomerular disease | 816 | 68 | 8.3 | 853 | 47 | 5.5 | 0.0228 | 0.66 | (0.46, 0.95) | 0.64 | (0.44, 0.94) | -0.03 | (-0.05, 0.00) | |
| Hypertensive/renovascular disease | 739 | 62 | 8.4 | 706 | 64 | 9.1 | 0.6492 | 1.08 | (0.77, 1.51) | 1.09 | (0.76, 1.57) | 0.01 | (-0.02, 0.04) | |
| Other/Unknown | 725 | 72 | 9.9 | 713 | 56 | 7.9 | 0.1667 | 0.79 | (0.57, 1.10) | 0.77 | (0.54, 1.11) | -0.02 | (-0.05, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8407 |
| <30 | 1151 | 121 | 10.5 | 1131 | 100 | 8.8 | 0.1772 | 0.84 | (0.65, 1.08) | 0.83 | (0.62, 1.09) | -0.02 | (-0.04, 0.01) | |
| 30 to <45 | 1461 | 122 | 8.4 | 1467 | 107 | 7.3 | 0.2870 | 0.87 | (0.68, 1.12) | 0.86 | (0.66, 1.13) | -0.01 | (-0.03, 0.01) | |
| >=45 | 693 | 64 | 9.2 | 706 | 50 | 7.1 | 0.1411 | 0.77 | (0.54, 1.09) | 0.75 | (0.51, 1.10) | -0.02 | (-0.05, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9495 |
| Normal (<30) | 663 | 66 | 10.0 | 665 | 53 | 8.0 | 0.2054 | 0.80 | (0.57, 1.13) | 0.78 | (0.54, 1.14) | -0.02 | (-0.05, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 76 | 8.1 | 927 | 65 | 7.0 | 0.3696 | 0.86 | (0.63, 1.19) | 0.85 | (0.61, 1.21) | -0.01 | (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 165 | 9.7 | 1712 | 139 | 8.1 | 0.1097 | 0.84 | (0.68, 1.04) | 0.82 | (0.65, 1.04) | -0.02 | (-0.03, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Surgical and medical procedures

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7433 |
| Low, moderate or high | 833 | 77 | 9.2 | 839 | 62 | 7.4 | 0.1698 | 0.80 | (0.58, 1.10) | 0.78 | (0.55, 1.11) | -0.02 | (-0.05, 0.01) | |
| Very high | 2472 | 230 | 9.3 | 2465 | 195 | 7.9 | 0.0809 | 0.85 | (0.71, 1.02) | 0.84 | (0.69, 1.02) | -0.01 | (-0.03, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.9755 |
| No | 508 | 56 | 11.0 | 473 | 44 | 9.3 | 0.3733 | 0.84 | (0.58, 1.23) | 0.83 | (0.55, 1.26) | -0.02 | (-0.05, 0.02) | |
| Yes | 2797 | 251 | 9.0 | 2831 | 213 | 7.5 | 0.0480 | 0.84 | (0.70, <1.00) | 0.83 | (0.68, 1.00) | -0.01 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9687 |
| No | 1940 | 154 | 7.9 | 1908 | 126 | 6.6 | 0.1111 | 0.83 | (0.66, 1.04) | 0.82 | (0.64, 1.05) | -0.01 | (-0.03, 0.00) | |
| Yes | 1365 | 153 | 11.2 | 1396 | 131 | 9.4 | 0.1145 | 0.84 | (0.67, 1.04) | 0.82 | (0.64, 1.05) | -0.02 | (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8011 |
| No | 1852 | 132 | 7.1 | 1942 | 115 | 5.9 | 0.1324 | 0.83 | (0.65, 1.06) | 0.82 | (0.63, 1.06) | -0.01 | (-0.03, 0.00) | |
| Yes | 1453 | 175 | 12.0 | 1362 | 142 | 10.4 | 0.1747 | 0.87 | (0.70, 1.07) | 0.85 | (0.67, 1.08) | -0.02 | (-0.04, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 236 | 7.1 | 3304 | 230 | 7.0 | 0.7757 | 0.97 (0.82, 1.16) | 0.97 (0.81, 1.17) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 228 | 6.9 | 3304 | 209 | 6.3 | 0.3486 | 0.92 (0.76, 1.10) | 0.91 (0.75, 1.11) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Investigations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 222 | 6.7 | 3304 | 190 | 5.8 | 0.1042 | 0.86 (0.71, 1.03) | 0.85 (0.69, 1.03) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 216 | 6.5 | 3304 | 181 | 5.5 | 0.0705 | 0.84 (0.69, | 1.02) | 0.83 (0.68, 1.02) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 184 | 5.6 | 3304 | 186 | 5.6 | 0.9124 | 1.01 (0.83, 1.23) | 1.01 (0.82, 1.25) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 126 | 3.8 | 3304 | 117 | 3.5 | 0.5580 | 0.93 (0.73, 1.19) | 0.93 (0.72, 1.20) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 98 | 3.0 | 3304 | 80 | 2.4 | 0.1720 | 0.82 (0.61, 1.09) | 0.81 (0.60, 1.10) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 97 | 2.9 | 3304 | 58 | 1.8 | 0.0015 | 0.60 (0.43, 0.83) | 0.59 (0.43, 0.82) | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | 0.5982 |
| Male | 2210 | 63 | 2.9 | 2207 | 40 | 1.8 | 0.0222 | 0.64 (0.43, 0.94) | 0.63 (0.42, 0.94) | -0.01 (-0.02, 0.00) | |
| Female | 1095 | 34 | 3.1 | 1097 | 18 | 1.6 | 0.0243 | 0.53 (0.30, 0.93) | 0.52 (0.29, 0.93) | -0.01 (-0.03, 0.00) | |
| Age [years] | | | | | | | | | | | 0.4613 |
| <65 | 1501 | 28 | 1.9 | 1501 | 20 | 1.3 | 0.2444 | 0.71 (0.40, 1.26) | 0.71 (0.40, 1.27) | -0.01 (-0.01, 0.00) | |
| >=65 | 1804 | 69 | 3.8 | 1803 | 38 | 2.1 | 0.0024 | 0.55 (0.37, 0.81) | 0.54 (0.36, 0.81) | -0.02 (-0.03,-0.01) | |
| Region | | | | | | | | | | | 0.3282 |
| North America | 873 | 27 | 3.1 | 844 | 11 | 1.3 | 0.0117 | 0.42 (0.21, 0.84) | 0.41 (0.20, 0.84) | -0.02 (-0.03, 0.00) | |
| Europe | 1304 | 54 | 4.1 | 1344 | 31 | 2.3 | 0.0074 | 0.56 (0.36, 0.86) | 0.55 (0.35, 0.86) | -0.02 (-0.03, 0.00) | |
| Japan | 308 | 6 | 1.9 | 304 | 5 | 1.6 | 0.7776 | 0.84 (0.26, 2.74) | 0.84 (0.25, 2.79) | 0.00 (-0.02, 0.02) | |
| Other Asia | 820 | 10 | 1.2 | 812 | 11 | 1.4 | 0.8086 | 1.11 (0.47, 2.60) | 1.11 (0.47, 2.63) | 0.00 (-0.01, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.3874 |
| Diabetic | 1515 | 48 | 3.2 | 1525 | 33 | 2.2 | 0.0856 | 0.68 (0.44, 1.06) | 0.68 (0.43, 1.06) | -0.01 (-0.02, 0.00) | |
| Non-diabetic | 1790 | 49 | 2.7 | 1779 | 25 | 1.4 | 0.0052 | 0.51 (0.32, 0.83) | 0.51 (0.31, 0.82) | -0.01 (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.9276 |
| <30 | 1961 | 57 | 2.9 | 1955 | 33 | 1.7 | 0.0109 | 0.58 (0.38, 0.89) | 0.57 (0.37, 0.88) | -0.01 (-0.02, 0.00) | |
| >=30 | 1337 | 40 | 3.0 | 1340 | 24 | 1.8 | 0.0420 | 0.60 (0.36, 0.99) | 0.59 (0.35, 0.99) | -0.01 (-0.02, 0.00) | |
| Prior CV disease | | | | | | | | | | | 0.7934 |
| No | 2401 | 54 | 2.2 | 2443 | 32 | 1.3 | 0.0133 | 0.58 (0.38, 0.90) | 0.58 (0.37, 0.90) | -0.01 (-0.02, 0.00) | |
| Yes | 904 | 43 | 4.8 | 861 | 26 | 3.0 | 0.0599 | 0.63 (0.39, 1.02) | 0.62 (0.38, 1.02) | -0.02 (-0.04, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.1310 |
| <130 | 1208 | 37 | 3.1 | 1190 | 15 | 1.3 | 0.0024 | 0.41 (0.23, 0.75) | 0.40 (0.22, 0.74) | -0.02 (-0.03,-0.01) | |
| >=130 | 2097 | 60 | 2.9 | 2114 | 43 | 2.0 | 0.0823 | 0.71 (0.48, 1.05) | 0.70 (0.47, 1.05) | -0.01 (-0.02, 0.00) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | 0.5431 |
| <75 | 1286 | 48 | 3.7 | 1294 | 25 | 1.9 | 0.0058 | 0.52 (0.32, 0.83) | 0.51 (0.31, 0.83) | -0.02 (-0.03,-0.01) | |
| 75 to <85 | 1033 | 17 | 1.6 | 1019 | 14 | 1.4 | 0.6138 | 0.83 (0.41, 1.68) | 0.83 (0.41, 1.70) | 0.00 (-0.01, 0.01) | |
| >=85 | 986 | 32 | 3.2 | 991 | 19 | 1.9 | 0.0625 | 0.59 (0.34, 1.04) | 0.58 (0.33, 1.04) | -0.01 (-0.03, 0.00) | |
| History of heart failure | | | | | | | | | | | 0.4577 |
| No | 2970 | 75 | 2.5 | 2979 | 48 | 1.6 | 0.0132 | 0.64 (0.45, 0.91) | 0.63 (0.44, 0.91) | -0.01 (-0.02, 0.00) | |
| Yes | 334 | 22 | 6.6 | 324 | 10 | 3.1 | 0.0369 | 0.47 (0.23, 0.97) | 0.45 (0.21, 0.97) | -0.04 (-0.07, 0.00) | |
| History of renal disease | | | | | | | | | | | 0.6269 |
| Diabetic kidney disease | 1025 | 31 | 3.0 | 1032 | 23 | 2.2 | 0.2591 | 0.74 (0.43, 1.25) | 0.73 (0.42, 1.26) | -0.01 (-0.02, 0.01) | |
| Glomerular disease | 816 | 16 | 2.0 | 853 | 11 | 1.3 | 0.2772 | 0.66 (0.31, 1.41) | 0.65 (0.30, 1.42) | -0.01 (-0.02, 0.01) | |
| Hypertensive/renovascular disease | 739 | 27 | 3.7 | 706 | 15 | 2.1 | 0.0837 | 0.58 (0.31, 1.08) | 0.57 (0.30, 1.09) | -0.02 (-0.03, 0.00) | |
| Other/Unknown | 725 | 23 | 3.2 | 713 | 9 | 1.3 | 0.0141 | 0.40 (0.19, 0.85) | 0.39 (0.18, 0.85) | -0.02 (-0.03, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.5277 |
| <30 | 1151 | 34 | 3.0 | 1131 | 24 | 2.1 | 0.2068 | 0.72 (0.43, 1.20) | 0.71 (0.42, 1.21) | -0.01 (-0.02, 0.00) | |
| 30 to <45 | 1461 | 42 | 2.9 | 1467 | 25 | 1.7 | 0.0342 | 0.59 (0.36, 0.97) | 0.59 (0.36, 0.97) | -0.01 (-0.02, 0.00) | |
| >=45 | 693 | 21 | 3.0 | 706 | 9 | 1.3 | 0.0234 | 0.42 (0.19, 0.91) | 0.41 (0.19, 0.91) | -0.02 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.4785 |
| Normal (<30) | 663 | 23 | 3.5 | 665 | 11 | 1.7 | 0.0363 | 0.48 (0.23, 0.97) | 0.47 (0.23, 0.97) | -0.02 (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 937 | 32 | 3.4 | 927 | 16 | 1.7 | 0.0213 | 0.51 (0.28, 0.91) | 0.50 (0.27, 0.91) | -0.02 (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 1705 | 42 | 2.5 | 1712 | 31 | 1.8 | 0.1871 | 0.74 (0.46, 1.16) | 0.73 (0.46, 1.17) | -0.01 (-0.02, 0.00) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | 0.3459 |
| Low, moderate or high | 833 | 30 | 3.6 | 839 | 14 | 1.7 | 0.0136 | 0.46 | (0.25, | 0.87) | 0.45 | (0.24, 0.86) | -0.02 | (-0.03, 0.00) | |
| Very high | 2472 | 67 | 2.7 | 2465 | 44 | 1.8 | 0.0283 | 0.66 | (0.45, | 0.96) | 0.65 | (0.44, 0.96) | -0.01 | (-0.02, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | | 0.6702 |
| No | 508 | 17 | 3.3 | 473 | 11 | 2.3 | 0.3373 | 0.69 | (0.33, | 1.47) | 0.69 | (0.32, 1.48) | -0.01 | (-0.03, 0.01) | |
| Yes | 2797 | 80 | 2.9 | 2831 | 47 | 1.7 | 0.0024 | 0.58 | (0.41, | 0.83) | 0.57 | (0.40, 0.83) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | 0.4914 |
| No | 1940 | 39 | 2.0 | 1908 | 26 | 1.4 | 0.1191 | 0.68 | (0.41, | 1.11) | 0.67 | (0.41, 1.11) | -0.01 | (-0.01, 0.00) | |
| Yes | 1365 | 58 | 4.2 | 1396 | 32 | 2.3 | 0.0038 | 0.54 | (0.35, | 0.83) | 0.53 | (0.34, 0.82) | -0.02 | (-0.03,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | 0.7480 |
| No | 1852 | 45 | 2.4 | 1942 | 27 | 1.4 | 0.0190 | 0.57 | (0.36, | 0.92) | 0.57 | (0.35, 0.92) | -0.01 | (-0.02, 0.00) | |
| Yes | 1453 | 52 | 3.6 | 1362 | 31 | 2.3 | 0.0412 | 0.64 | (0.41, | 0.99) | 0.63 | (0.40, 0.99) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 86 | 2.6 | 3304 | 86 | 2.6 | 0.9984 | 1.00 (0.74, 1.34) | 1.00 (0.74, 1.35) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 66 | 2.0 | 3304 | 49 | 1.5 | 0.1101 | 0.74 (0.51, 1.07) | 0.74 (0.51, 1.07) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 57 | 1.7 | 3304 | 48 | 1.5 | 0.3768 | 0.84 (0.58, 1.23) | 0.84 (0.57, 1.24) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 47 | 1.4 | 3304 | 47 | 1.4 | 0.9988 | 1.00 (0.67, 1.49) | 1.00 (0.67, 1.50) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 30 | 0.9 | 3304 | 36 | 1.1 | 0.4572 | 1.20 (0.74, 1.94) | 1.20 (0.74, 1.96) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 332 | 10.0 | 3304 | 319 | 9.7 | 0.5943 | 0.96 (0.83, 1.11) | 0.96 (0.81, 1.13) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Surgical and medical procedures

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 304 | 9.2 | 3304 | 255 | 7.7 | 0.0306 | 0.84 (0.72, 0.98) | 0.83 (0.69, 0.98) | -0.01 (-0.03, 0.00) | |
| Sex | | | | | | | | | | | 0.1478 |
| Male | 2210 | 203 | 9.2 | 2207 | 184 | 8.3 | 0.3187 | 0.91 (0.75, 1.10) | 0.90 (0.73, 1.11) | -0.01 (-0.03, 0.01) | |
| Female | 1095 | 101 | 9.2 | 1097 | 71 | 6.5 | 0.0166 | 0.70 (0.52, 0.94) | 0.68 (0.50, 0.93) | -0.03 (-0.05,-0.01) | |
| Age [years] | | | | | | | | | | | 0.7275 |
| <65 | 1501 | 109 | 7.3 | 1501 | 88 | 5.9 | 0.1217 | 0.81 (0.62, 1.06) | 0.80 (0.59, 1.06) | -0.01 (-0.03, 0.00) | |
| >=65 | 1804 | 195 | 10.8 | 1803 | 167 | 9.3 | 0.1221 | 0.86 (0.70, 1.04) | 0.84 (0.68, 1.05) | -0.02 (-0.04, 0.00) | |
| Region | | | | | | | | | | | 0.6865 |
| North America | 873 | 53 | 6.1 | 844 | 50 | 5.9 | 0.8981 | 0.98 (0.67, 1.42) | 0.97 (0.65, 1.45) | 0.00 (-0.02, 0.02) | |
| Europe | 1304 | 159 | 12.2 | 1344 | 137 | 10.2 | 0.1025 | 0.84 (0.67, 1.04) | 0.82 (0.64, 1.04) | -0.02 (-0.04, 0.00) | |
| Japan | 308 | 51 | 16.6 | 304 | 35 | 11.5 | 0.0725 | 0.70 (0.47, 1.04) | 0.66 (0.41, 1.04) | -0.05 (-0.11, 0.00) | |
| Other Asia | 820 | 41 | 5.0 | 812 | 33 | 4.1 | 0.3635 | 0.81 (0.52, 1.27) | 0.80 (0.50, 1.29) | -0.01 (-0.03, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.6920 |
| Diabetic | 1515 | 172 | 11.4 | 1525 | 141 | 9.2 | 0.0559 | 0.81 (0.66, 1.01) | 0.80 (0.63, 1.01) | -0.02 (-0.04, 0.00) | |
| Non-diabetic | 1790 | 132 | 7.4 | 1779 | 114 | 6.4 | 0.2546 | 0.87 (0.68, 1.11) | 0.86 (0.66, 1.11) | -0.01 (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.4558 |
| <30 | 1961 | 183 | 9.3 | 1955 | 146 | 7.5 | 0.0355 | 0.80 (0.65, 0.99) | 0.78 (0.62, 0.98) | -0.02 (-0.04, 0.00) | |
| >=30 | 1337 | 119 | 8.9 | 1340 | 108 | 8.1 | 0.4349 | 0.91 (0.71, 1.16) | 0.90 (0.68, 1.18) | -0.01 (-0.03, 0.01) | |
| Prior CV disease | | | | | | | | | | | 0.6302 |
| No | 2401 | 179 | 7.5 | 2443 | 159 | 6.5 | 0.1959 | 0.87 (0.71, 1.07) | 0.86 (0.69, 1.08) | -0.01 (-0.02, 0.00) | |
| Yes | 904 | 125 | 13.8 | 861 | 96 | 11.1 | 0.0893 | 0.81 (0.63, 1.03) | 0.78 (0.59, 1.04) | -0.03 (-0.06, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.5057 |
| <130 | 1208 | 112 | 9.3 | 1190 | 86 | 7.2 | 0.0689 | 0.78 (0.60, 1.02) | 0.76 (0.57, 1.02) | -0.02 (-0.04, 0.00) | |
| >=130 | 2097 | 192 | 9.2 | 2114 | 169 | 8.0 | 0.1782 | 0.87 (0.72, 1.06) | 0.86 (0.69, 1.07) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Surgical and medical procedures

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6295 |
| <75 | 1286 | 149 | 11.6 | 1294 | 116 | 9.0 | 0.0283 | 0.77 | (0.61, 0.97) | 0.75 | (0.58, 0.97) | -0.03 | (-0.05, 0.00) | |
| 75 to <85 | 1033 | 84 | 8.1 | 1019 | 73 | 7.2 | 0.4096 | 0.88 | (0.65, 1.19) | 0.87 | (0.63, 1.21) | -0.01 | (-0.03, 0.01) | |
| >=85 | 986 | 71 | 7.2 | 991 | 66 | 6.7 | 0.6359 | 0.92 | (0.67, 1.28) | 0.92 | (0.65, 1.30) | -0.01 | (-0.03, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.6068 |
| No | 2970 | 244 | 8.2 | 2979 | 210 | 7.0 | 0.0903 | 0.86 | (0.72, 1.02) | 0.85 | (0.70, 1.03) | -0.01 | (-0.03, 0.00) | |
| Yes | 334 | 60 | 18.0 | 324 | 45 | 13.9 | 0.1536 | 0.77 | (0.54, 1.10) | 0.74 | (0.48, 1.12) | -0.04 | (-0.10, 0.02) | |
| History of renal disease | | | | | | | | | | | | | | 0.3327 |
| Diabetic kidney disease | 1025 | 104 | 10.1 | 1032 | 90 | 8.7 | 0.2687 | 0.86 | (0.66, 1.12) | 0.85 | (0.63, 1.14) | -0.01 | (-0.04, 0.01) | |
| Glomerular disease | 816 | 68 | 8.3 | 853 | 47 | 5.5 | 0.0228 | 0.66 | (0.46, 0.95) | 0.64 | (0.44, 0.94) | -0.03 | (-0.05, 0.00) | |
| Hypertensive/renovascular disease | 739 | 62 | 8.4 | 706 | 62 | 8.8 | 0.7902 | 1.05 | (0.75, 1.47) | 1.05 | (0.73, 1.52) | 0.00 | (-0.02, 0.03) | |
| Other/Unknown | 725 | 70 | 9.7 | 713 | 56 | 7.9 | 0.2272 | 0.81 | (0.58, 1.14) | 0.80 | (0.55, 1.15) | -0.02 | (-0.05, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8975 |
| <30 | 1151 | 119 | 10.3 | 1131 | 100 | 8.8 | 0.2248 | 0.86 | (0.66, 1.10) | 0.84 | (0.64, 1.11) | -0.01 | (-0.04, 0.01) | |
| 30 to <45 | 1461 | 122 | 8.4 | 1467 | 105 | 7.2 | 0.2275 | 0.86 | (0.67, 1.10) | 0.85 | (0.64, 1.11) | -0.01 | (-0.03, 0.01) | |
| >=45 | 693 | 63 | 9.1 | 706 | 50 | 7.1 | 0.1680 | 0.78 | (0.55, 1.11) | 0.76 | (0.52, 1.12) | -0.02 | (-0.05, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9569 |
| Normal (<30) | 663 | 66 | 10.0 | 665 | 53 | 8.0 | 0.2054 | 0.80 | (0.57, 1.13) | 0.78 | (0.54, 1.14) | -0.02 | (-0.05, 0.01) | |
| Microalbuminuria (30 to <=300) | 937 | 75 | 8.0 | 927 | 63 | 6.8 | 0.3192 | 0.85 | (0.62, 1.17) | 0.84 | (0.59, 1.19) | -0.01 | (-0.04, 0.01) | |
| Macroalbuminuria (>300) | 1705 | 163 | 9.6 | 1712 | 139 | 8.1 | 0.1379 | 0.85 | (0.68, 1.05) | 0.84 | (0.66, 1.06) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Surgical and medical procedures

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7324 |
| Low, moderate or high | 833 | 77 | 9.2 | 839 | 62 | 7.4 | 0.1698 | 0.80 | (0.58, 1.10) | 0.78 | (0.55, 1.11) | -0.02 | (-0.05, 0.01) | |
| Very high | 2472 | 227 | 9.2 | 2465 | 193 | 7.8 | 0.0884 | 0.85 | (0.71, 1.02) | 0.84 | (0.69, 1.03) | -0.01 | (-0.03, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | | | | 0.9933 |
| No | 508 | 55 | 10.8 | 473 | 43 | 9.1 | 0.3649 | 0.84 | (0.57, 1.23) | 0.82 | (0.54, 1.25) | -0.02 | (-0.05, 0.02) | |
| Yes | 2797 | 249 | 8.9 | 2831 | 212 | 7.5 | 0.0531 | 0.84 | (0.71, >1.00) | 0.83 | (0.68, 1.00) | -0.01 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9361 |
| No | 1940 | 151 | 7.8 | 1908 | 125 | 6.6 | 0.1386 | 0.84 | (0.67, 1.06) | 0.83 | (0.65, 1.06) | -0.01 | (-0.03, 0.00) | |
| Yes | 1365 | 153 | 11.2 | 1396 | 130 | 9.3 | 0.1005 | 0.83 | (0.67, 1.04) | 0.81 | (0.64, 1.04) | -0.02 | (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9042 |
| No | 1852 | 129 | 7.0 | 1942 | 114 | 5.9 | 0.1684 | 0.84 | (0.66, 1.08) | 0.83 | (0.64, 1.08) | -0.01 | (-0.03, 0.00) | |
| Yes | 1453 | 175 | 12.0 | 1362 | 141 | 10.4 | 0.1554 | 0.86 | (0.70, 1.06) | 0.84 | (0.67, 1.07) | -0.02 | (-0.04, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 228 | 6.9 | 3304 | 209 | 6.3 | 0.3486 | 0.92 (0.76, 1.10) | 0.91 (0.75, 1.11) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Investigations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 214 | 6.5 | 3304 | 182 | 5.5 | 0.0978 | 0.85 (0.70, 1.03) | 0.84 (0.69, 1.03) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 211 | 6.4 | 3304 | 180 | 5.4 | 0.1067 | 0.85 (0.70, 1.03) | 0.84 (0.69, 1.04) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 137 | 4.1 | 3304 | 127 | 3.8 | 0.5316 | 0.93 (0.73, 1.17) | 0.92 (0.72, 1.18) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 126 | 3.8 | 3304 | 117 | 3.5 | 0.5580 | 0.93 | (0.73, 1.19) | 0.93 (0.72, 1.20) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 118 | 3.6 | 3304 | 111 | 3.4 | 0.6394 | 0.94 (0.73, 1.21) | 0.94 (0.72, 1.22) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 108 | 3.3 | 3304 | 114 | 3.5 | 0.6804 | 1.06 (0.82, 1.37) | 1.06 (0.81, 1.38) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 96 | 2.9 | 3304 | 76 | 2.3 | 0.1228 | 0.79 (0.59, 1.07) | 0.79 (0.58, 1.07) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 68 | 2.1 | 3304 | 47 | 1.4 | 0.0484 | 0.69 (0.48, <1.00) | 0.69 (0.47, 1.00) | -0.01 (-0.01, 0.00) | |
| Sex | | | | | | | | | | | 0.5830 |
| Male | 2210 | 43 | 1.9 | 2207 | 32 | 1.4 | 0.2023 | 0.75 (0.47, 1.17) | 0.74 (0.47, 1.18) | 0.00 (-0.01, 0.00) | |
| Female | 1095 | 25 | 2.3 | 1097 | 15 | 1.4 | 0.1092 | 0.60 (0.32, 1.13) | 0.59 (0.31, 1.13) | -0.01 (-0.02, 0.00) | |
| Age [years] | | | | | | | | | | | 0.6955 |
| <65 | 1501 | 18 | 1.2 | 1501 | 14 | 0.9 | 0.4771 | 0.78 (0.39, 1.56) | 0.78 (0.38, 1.57) | 0.00 (-0.01, 0.00) | |
| >=65 | 1804 | 50 | 2.8 | 1803 | 33 | 1.8 | 0.0594 | 0.66 (0.43, 1.02) | 0.65 (0.42, 1.02) | -0.01 (-0.02, 0.00) | |
| Region | | | | | | | | | | | 0.3678 |
| North America | 873 | 18 | 2.1 | 844 | 10 | 1.2 | 0.1514 | 0.57 (0.27, 1.24) | 0.57 (0.26, 1.24) | -0.01 (-0.02, 0.00) | |
| Europe | 1304 | 39 | 3.0 | 1344 | 23 | 1.7 | 0.0295 | 0.57 (0.34, 0.95) | 0.56 (0.34, 0.95) | -0.01 (-0.02, 0.00) | |
| Japan | 308 | 3 | 1.0 | 304 | 4 | 1.3 | 0.6910 | 1.35 (0.30, 5.99) | 1.36 (0.30, 6.11) | 0.00 (-0.01, 0.02) | |
| Other Asia | 820 | 8 | 1.0 | 812 | 10 | 1.2 | 0.6206 | 1.26 (0.50, 3.18) | 1.27 (0.50, 3.22) | 0.00 (-0.01, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.1718 |
| Diabetic | 1515 | 33 | 2.2 | 1525 | 29 | 1.9 | 0.5896 | 0.87 (0.53, 1.43) | 0.87 (0.53, 1.44) | 0.00 (-0.01, 0.01) | |
| Non-diabetic | 1790 | 35 | 2.0 | 1779 | 18 | 1.0 | 0.0198 | 0.52 (0.29, 0.91) | 0.51 (0.29, 0.91) | -0.01 (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.8118 |
| <30 | 1961 | 37 | 1.9 | 1955 | 26 | 1.3 | 0.1661 | 0.70 (0.43, 1.16) | 0.70 (0.42, 1.16) | -0.01 (-0.01, 0.00) | |
| >=30 | 1337 | 31 | 2.3 | 1340 | 20 | 1.5 | 0.1180 | 0.64 (0.37, 1.12) | 0.64 (0.36, 1.13) | -0.01 (-0.02, 0.00) | |
| Prior CV disease | | | | | | | | | | | 0.7585 |
| No | 2401 | 36 | 1.5 | 2443 | 27 | 1.1 | 0.2260 | 0.74 (0.45, 1.21) | 0.73 (0.44, 1.21) | 0.00 (-0.01, 0.00) | |
| Yes | 904 | 32 | 3.5 | 861 | 20 | 2.3 | 0.1307 | 0.66 (0.38, 1.14) | 0.65 (0.37, 1.14) | -0.01 (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.0309 |
| <130 | 1208 | 28 | 2.3 | 1190 | 10 | 0.8 | 0.0038 | 0.36 (0.18, 0.74) | 0.36 (0.17, 0.74) | -0.01 (-0.02, 0.00) | |
| >=130 | 2097 | 40 | 1.9 | 2114 | 37 | 1.8 | 0.7033 | 0.92 (0.59, 1.43) | 0.92 (0.58, 1.44) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | 0.5458 |
| <75 | 1286 | 32 | 2.5 | 1294 | 19 | 1.5 | 0.0627 | 0.59 (0.34, 1.04) | 0.58 (0.33, 1.04) | -0.01 (-0.02, 0.00) | |
| 75 to <85 | 1033 | 12 | 1.2 | 1019 | 12 | 1.2 | 0.9732 | 1.01 (0.46, 2.25) | 1.01 (0.45, 2.27) | 0.00 (-0.01, 0.01) | |
| >=85 | 986 | 24 | 2.4 | 991 | 16 | 1.6 | 0.1956 | 0.66 (0.35, 1.24) | 0.66 (0.35, 1.25) | -0.01 (-0.02, 0.00) | |
| History of heart failure | | | | | | | | | | | 0.4335 |
| No | 2970 | 52 | 1.8 | 2979 | 39 | 1.3 | 0.1652 | 0.75 (0.50, 1.13) | 0.74 (0.49, 1.13) | 0.00 (-0.01, 0.00) | |
| Yes | 334 | 16 | 4.8 | 324 | 8 | 2.5 | 0.1123 | 0.52 (0.22, 1.19) | 0.50 (0.21, 1.19) | -0.02 (-0.05, 0.01) | |
| History of renal disease | | | | | | | | | | | 0.4542 |
| Diabetic kidney disease | 1025 | 23 | 2.2 | 1032 | 20 | 1.9 | 0.6277 | 0.86 (0.48, 1.56) | 0.86 (0.47, 1.58) | 0.00 (-0.02, 0.01) | |
| Glomerular disease | 816 | 11 | 1.3 | 853 | 8 | 0.9 | 0.4298 | 0.70 (0.28, 1.72) | 0.69 (0.28, 1.73) | 0.00 (-0.01, 0.01) | |
| Hypertensive/renovascular disease | 739 | 17 | 2.3 | 706 | 13 | 1.8 | 0.5407 | 0.80 (0.39, 1.64) | 0.80 (0.38, 1.65) | 0.00 (-0.02, 0.01) | |
| Other/Unknown | 725 | 17 | 2.3 | 713 | 6 | 0.8 | 0.0231 | 0.36 (0.14, 0.91) | 0.35 (0.14, 0.90) | -0.02 (-0.03, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.4310 |
| <30 | 1151 | 25 | 2.2 | 1131 | 22 | 1.9 | 0.7029 | 0.90 (0.51, 1.58) | 0.89 (0.50, 1.59) | 0.00 (-0.01, 0.01) | |
| 30 to <45 | 1461 | 28 | 1.9 | 1467 | 18 | 1.2 | 0.1336 | 0.64 (0.36, 1.15) | 0.64 (0.35, 1.15) | -0.01 (-0.02, 0.00) | |
| >=45 | 693 | 15 | 2.2 | 706 | 7 | 1.0 | 0.0779 | 0.46 (0.19, 1.12) | 0.45 (0.18, 1.12) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.2009 |
| Normal (<30) | 663 | 18 | 2.7 | 665 | 8 | 1.2 | 0.0468 | 0.44 (0.19, 1.01) | 0.44 (0.19, 1.01) | -0.02 (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 937 | 21 | 2.2 | 927 | 11 | 1.2 | 0.0797 | 0.53 (0.26, 1.09) | 0.52 (0.25, 1.09) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 1705 | 29 | 1.7 | 1712 | 28 | 1.6 | 0.8814 | 0.96 (0.57, 1.61) | 0.96 (0.57, 1.62) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline KDIGO risk category | | | | | | | | | | | 0.1525 |
| Low, moderate or high | 833 | 21 | 2.5 | 839 | 9 | 1.1 | 0.0257 | 0.43 (0.20, 0.92) | 0.42 (0.19, 0.92) | -0.01 (-0.03, 0.00) | |
| Very high | 2472 | 47 | 1.9 | 2465 | 38 | 1.5 | 0.3313 | 0.81 (0.53, 1.24) | 0.81 (0.52, 1.24) | 0.00 (-0.01, 0.00) | |
| Baseline use of RAS inhibitor*** | | | | | | | | | | | 0.7563 |
| No | 508 | 14 | 2.8 | 473 | 8 | 1.7 | 0.2605 | 0.61 (0.26, 1.45) | 0.61 (0.25, 1.46) | -0.01 (-0.03, 0.01) | |
| Yes | 2797 | 54 | 1.9 | 2831 | 39 | 1.4 | 0.1037 | 0.71 (0.47, 1.07) | 0.71 (0.47, 1.07) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.3371 |
| No | 1940 | 25 | 1.3 | 1908 | 21 | 1.1 | 0.5915 | 0.85 (0.48, 1.52) | 0.85 (0.48, 1.53) | 0.00 (-0.01, 0.00) | |
| Yes | 1365 | 43 | 3.2 | 1396 | 26 | 1.9 | 0.0302 | 0.59 (0.37, 0.96) | 0.58 (0.36, 0.96) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.8090 |
| No | 1852 | 27 | 1.5 | 1942 | 21 | 1.1 | 0.2996 | 0.74 (0.42, 1.31) | 0.74 (0.42, 1.31) | 0.00 (-0.01, 0.00) | |
| Yes | 1453 | 41 | 2.8 | 1362 | 26 | 1.9 | 0.1123 | 0.68 (0.42, 1.10) | 0.67 (0.41, 1.10) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 64 | 1.9 | 3304 | 45 | 1.4 | 0.0667 | 0.70 (0.48, 1.03) | 0.70 (0.48, 1.03) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 3305 | 57 | 1.7 | 3304 | 48 | 1.5 | 0.3768 | 0.84 (0.58, 1.23) | 0.84 (0.57, 1.24) | 0.00 (-0.01, 0.00) | | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3305 | 44 | 1.3 | 3304 | 41 | 1.2 | 0.7443 | 0.93 (0.61, 1.42) | 0.93 (0.61, 1.43) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.1.2.5**

R.1.2.5 Adverse events on PT level

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Gout

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 279 | 8.4 | 3304 | 239 | 7.2 | 0.0677 | 0.86 ( 0.73, 1.01) | 0.85 ( 0.71, 1.01) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Dehydration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 70 | 2.1 | 3304 | 75 | 2.3 | 0.6732 | 1.07 ( 0.78, 1.48) | 1.07 ( 0.77, 1.49) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypoglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 72 | 2.2 | 3304 | 69 | 2.1 | 0.7998 | 0.96 ( 0.69, 1.33) | 0.96 ( 0.69, 1.34) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Corona virus infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 120 | 3.6 | 3304 | 105 | 3.2 | 0.3100 | 0.88 ( 0.68, 1.13) | 0.87 ( 0.67, 1.14) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 50 | 1.5 | 3304 | 43 | 1.3 | 0.4657 | 0.86 ( 0.57, 1.29) | 0.86 ( 0.57, 1.29) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 37 | 1.1 | 3304 | 38 | 1.2 | 0.9065 | 1.03 ( 0.65, 1.61) | 1.03 ( 0.65, 1.62) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Neuropathy peripheral

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 45 | 1.4 | 3304 | 30 | 0.9 | 0.0817 | 0.67 ( 0.42, 1.06) | 0.66 ( 0.42, 1.06) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 36 | 1.1 | 3304 | 31 | 0.9 | 0.5401 | 0.86 ( 0.53, 1.39) | 0.86 ( 0.53, 1.39) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 51 | 1.5 | 3304 | 53 | 1.6 | 0.8421 | 1.04 ( 0.71, 1.52) | 1.04 ( 0.71, 1.53) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ischaemic cardiomyopathy

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 50 | 1.5 | 3304 | 42 | 1.3 | 0.4018 | 0.84 ( 0.56, 1.26) | 0.84 ( 0.55, 1.27) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 36 | 1.1 | 3304 | 41 | 1.2 | 0.5656 | 1.14 ( 0.73, 1.78) | 1.14 ( 0.73, 1.79) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 36 | 1.1 | 3304 | 23 | 0.7 | 0.0893 | 0.64 ( 0.38, 1.08) | 0.64 ( 0.38, 1.08) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood potassium increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 99 | 3.0 | 3304 | 83 | 2.5 | 0.2299 | 0.84 ( 0.63, 1.12) | 0.83 ( 0.62, 1.12) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood creatinine increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 69 | 2.1 | 3304 | 55 | 1.7 | 0.2050 | 0.80 ( 0.56, 1.13) | 0.79 ( 0.56, 1.14) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 135 | 4.1 | 3304 | 107 | 3.2 | 0.0670 | 0.79 ( 0.62, 1.02) | 0.79 ( 0.61, 1.02) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: End stage renal disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 40 | 1.2 | 3304 | 43 | 1.3 | 0.7393 | 1.08 ( 0.70, 1.65) | 1.08 ( 0.70, 1.66) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Gouty arthritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 45 | 1.4 | 3304 | 46 | 1.4 | 0.9148 | 1.02 ( 0.68, 1.54) | 1.02 ( 0.68, 1.55) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137. SAEs and protocol pre-specified non-serious AEs included.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Corona virus infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 120 | 3.6 | 3304 | 105 | 3.2 | 0.3100 | 0.88 ( 0.68, 1.13) | 0.87 ( 0.67, 1.14) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 50 | 1.5 | 3304 | 43 | 1.3 | 0.4657 | 0.86 ( 0.57, 1.29) | 0.86 ( 0.57, 1.29) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 37 | 1.1 | 3304 | 32 | 1.0 | 0.5460 | 0.87 ( 0.54, 1.39) | 0.86 ( 0.54, 1.39) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 51 | 1.5 | 3304 | 53 | 1.6 | 0.8421 | 1.04 ( 0.71, 1.52) | 1.04 ( 0.71, 1.53) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ischaemic cardiomyopathy

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 50 | 1.5 | 3304 | 42 | 1.3 | 0.4018 | 0.84 ( 0.56, 1.26) | 0.84 ( 0.55, 1.27) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 36 | 1.1 | 3304 | 41 | 1.2 | 0.5656 | 1.14 ( 0.73, 1.78) | 1.14 ( 0.73, 1.79) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 36 | 1.1 | 3304 | 23 | 0.7 | 0.0893 | 0.64 ( 0.38, 1.08) | 0.64 ( 0.38, 1.08) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood potassium increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 99 | 3.0 | 3304 | 83 | 2.5 | 0.2299 | 0.84 ( 0.63, 1.12) | 0.83 ( 0.62, 1.12) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood creatinine increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 64 | 1.9 | 3304 | 48 | 1.5 | 0.1277 | 0.75 ( 0.52, 1.09) | 0.75 ( 0.51, 1.09) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 135 | 4.1 | 3304 | 107 | 3.2 | 0.0670 | 0.79 ( 0.62, 1.02) | 0.79 ( 0.61, 1.02) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: End stage renal disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 40 | 1.2 | 3304 | 43 | 1.3 | 0.7393 | 1.08 ( 0.70, 1.65) | 1.08 ( 0.70, 1.66) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.1.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the final follow-up visit, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3305 | 36 | 1.1 | 3304 | 31 | 0.9 | 0.5401 | 0.86 ( 0.53, 1.39) | 0.86 ( 0.53, 1.39) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.137.
If adjudicated, the resulting preferred terms are presented.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
*** Defined as use of an ACEi, ARB, ARNi or renin inhibitor.
MedDRA version: 20.1. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.1.2.6**

R.1.2.6 Medical concepts for adverse events of special interest and other specific AEs

Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Broad BIcMQ 'Urinary bladder and tract malignancies', Broad BIcMQ 'Renal malignancies' | Urinary tract malignancy events (BIcMQ) | 40000010 | | 10004986 | Bladder adenocarcinoma recurrent |
| | | | | 10004987 | Bladder adenocarcinoma stage 0 |
| | | | | 10004988 | Bladder adenocarcinoma stage I |
| | | | | 10004989 | Bladder adenocarcinoma stage II |
| | | | | 10004990 | Bladder adenocarcinoma stage III |
| | | | | 10004991 | Bladder adenocarcinoma stage IV |
| | | | | 10004992 | Bladder adenocarcinoma stage unspecified |
| | | | | 10005003 | Bladder cancer |
| | | | | 10005005 | Bladder cancer recurrent |
| | | | | 10005006 | Bladder cancer stage 0, with cancer in situ |
| | | | | 10005007 | Bladder cancer stage 0, without cancer in situ |
| | | | | 10005008 | Bladder cancer stage I, with cancer in situ |
| | | | | 10005009 | Bladder cancer stage I, without cancer in situ |
| | | | | 10005010 | Bladder cancer stage II |
| | | | | 10005011 | Bladder cancer stage III |
| | | | | 10005012 | Bladder cancer stage IV |
| | | | | 10005056 | Bladder neoplasm |
| | | | | 10005075 | Bladder squamous cell carcinoma recurrent |
| | | | | 10005076 | Bladder squamous cell carcinoma stage 0 |
| | | | | 10005077 | Bladder squamous cell carcinoma stage I |
| | | | | 10005078 | Bladder squamous cell carcinoma stage II |
| | | | | 10005079 | Bladder squamous cell carcinoma stage III |
| | | | | 10005080 | Bladder squamous cell carcinoma stage IV |
| | | | | 10005081 | Bladder squamous cell carcinoma stage unspecified |
| | | | | 10005084 | Bladder transitional cell carcinoma |
| | | | | 10009253 | Clear cell sarcoma of the kidney |
| | | | | 10026426 | Malignant neoplasm of renal pelvis |
| | | | | 10029145 | Nephroblastoma |
| | | | | 10038389 | Renal cancer |
| | | | | 10038390 | Renal cancer recurrent |
| | | | | 10038391 | Renal cancer stage I |
| | | | | 10038392 | Renal cancer stage II |
| | | | | 10038393 | Renal cancer stage III |

Analyses are based on 1245.137.
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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code Scope | Preferred term code | Preferred term |
|---|---|---|---|---|
| Broad BIcMQ 'Urinary bladder and tract malignancies', Broad BIcMQ 'Renal malignancies' | Urinary tract malignancy events (BIcMQ) | 40000010 | 10038394 | Renal cancer stage IV |
| | | | 10038410 | Renal cell carcinoma recurrent |
| | | | 10038411 | Renal cell carcinoma stage I |
| | | | 10038412 | Renal cell carcinoma stage II |
| | | | 10038413 | Renal cell carcinoma stage III |
| | | | 10038414 | Renal cell carcinoma stage IV |
| | | | 10039019 | Rhabdoid tumour of the kidney |
| | | | 10044406 | Transitional cell cancer of renal pelvis and ureter metastatic |
| | | | 10044407 | Transitional cell cancer of the renal pelvis and ureter |
| | | | 10044408 | Transitional cell cancer of the renal pelvis and ureter localised |
| | | | 10044410 | Transitional cell cancer of the renal pelvis and ureter recurrent |
| | | | 10044411 | Transitional cell cancer of the renal pelvis and ureter regional |
| | | | 10044412 | Transitional cell carcinoma |
| | | | 10050018 | Renal cancer metastatic |
| | | | 10050513 | Metastatic renal cell carcinoma |
| | | | 10051690 | Urinary bladder sarcoma |
| | | | 10057352 | Metastatic carcinoma of the bladder |
| | | | 10061183 | Genitourinary tract neoplasm |
| | | | 10061272 | Malignant urinary tract neoplasm |
| | | | 10061396 | Urinary tract carcinoma in situ |
| | | | 10061398 | Urinary tract neoplasm |
| | | | 10061482 | Renal neoplasm |
| | | | 10061872 | Non-renal cell carcinoma of kidney |
| | | | 10066749 | Bladder transitional cell carcinoma stage 0 |
| | | | 10066750 | Bladder transitional cell carcinoma recurrent |
| | | | 10066751 | Bladder transitional cell carcinoma stage I |
| | | | 10066752 | Bladder transitional cell carcinoma stage IV |
| | | | 10066753 | Bladder transitional cell carcinoma stage II |
| | | | 10066754 | Bladder transitional cell carcinoma stage III |

Analyses are based on 1245.137.
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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code Scope | Preferred term code | Preferred term |
|---|---|---|---|---|
| Broad BIcMQ 'Urinary bladder and tract malignancies', Broad BIcMQ 'Renal malignancies' | Urinary tract malignancy events (BIcMQ) | 40000010 | 10067943 | Hereditary papillary renal carcinoma |
| | | | 10067944 | Hereditary leiomyomatosis renal cell carcinoma |
| | | | 10067946 | Renal cell carcinoma |
| | | | 10069359 | Leukaemic infiltration renal |
| | | | 10071080 | Transitional cell carcinoma metastatic |
| | | | 10071664 | Bladder transitional cell carcinoma metastatic |
| | | | 10073251 | Clear cell renal cell carcinoma |
| | | | 10074419 | Malignant genitourinary tract neoplasm |
| | | | 10077051 | Transitional cell carcinoma recurrent |
| | | | 10077166 | Genitourinary melanoma |
| | | | 10078341 | Neuroendocrine carcinoma of the bladder |
| | | | 10078493 | Papillary renal cell carcinoma |
| Narrow BIcMQ 'Bone fractures' | Bone fracture events (BIcMQ) | 40000012 | 10000397 | Acetabulum fracture |
| | | | 10002544 | Ankle fracture |
| | | | 10009245 | Clavicle fracture |
| | | | 10009506 | Closed fracture manipulation |
| | | | 10010149 | Complicated fracture |
| | | | 10010214 | Compression fracture |
| | | | 10014487 | Elevation skull fracture |
| | | | 10015741 | External fixation of fracture |
| | | | 10016042 | Facial bones fracture |
| | | | 10016450 | Femoral neck fracture |
| | | | 10016454 | Femur fracture |
| | | | 10016667 | Fibula fracture |
| | | | 10016747 | Flail chest |
| | | | 10016970 | Foot fracture |
| | | | 10016997 | Forearm fracture |
| | | | 10017076 | Fracture |
| | | | 10017107 | Fracture of clavicle due to birth trauma |
| | | | 10017290 | Fractured ischium |
| | | | 10017296 | Fractured maxilla elevation |
| | | | 10017308 | Fractured sacrum |
| | | | 10017310 | Fractured skull depressed |
| | | | 10018720 | Greenstick fracture |
| | | | 10019114 | Hand fracture |
| | | | 10020100 | Hip fracture |

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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code Scope | Preferred term code | Preferred term |
|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures' | Bone fracture events (BIcMQ) | 40000012 | 10020462 | Humerus fracture |
| | | | 10021343 | Ilium fracture |
| | | | 10022576 | Internal fixation of fracture |
| | | | 10023149 | Jaw fracture |
| | | | 10028200 | Multiple fractures |
| | | | 10030527 | Open fracture |
| | | | 10030682 | Open reduction of fracture |
| | | | 10031290 | Osteoporotic fracture |
| | | | 10034122 | Patella fracture |
| | | | 10034156 | Pathological fracture |
| | | | 10037802 | Radius fracture |
| | | | 10039117 | Rib fracture |
| | | | 10039579 | Scapula fracture |
| | | | 10040960 | Skull fractured base |
| | | | 10041541 | Spinal compression fracture |
| | | | 10041569 | Spinal fracture |
| | | | 10042015 | Sternal fracture |
| | | | 10042212 | Stress fracture |
| | | | 10043827 | Tibia fracture |
| | | | 10045375 | Ulna fracture |
| | | | 10048049 | Wrist fracture |
| | | | 10049164 | Fractured coccyx |
| | | | 10049514 | Traumatic fracture |
| | | | 10049946 | Cervical vertebral fracture |
| | | | 10049947 | Lumbar vertebral fracture |
| | | | 10049948 | Thoracic vertebral fracture |
| | | | 10052614 | Comminuted fracture |
| | | | 10053206 | Fracture displacement |
| | | | 10053962 | Epiphyseal fracture |
| | | | 10057147 | Fracture debridement |
| | | | 10057609 | Fracture reduction |
| | | | 10059362 | Fractured zygomatic arch elevation |
| | | | 10061161 | Pelvic fracture |
| | | | 10061365 | Skull fracture |
| | | | 10061394 | Upper limb fracture |
| | | | 10061599 | Lower limb fracture |
| | | | 10061959 | Fracture treatment |
| | | | 10064210 | Bone fissure |
| | | | 10064211 | Bone fragmentation |
| | | | 10066094 | Torus fracture |
| | | | 10066184 | Avulsion fracture |

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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code Scope | Preferred term code | Preferred term |
|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures' | Bone fracture events (BIcMQ) | 40000012 | 10066386 | Impacted fracture |
| | | | 10069066 | Intramedullary rod insertion |
| | | | 10069135 | Periprosthetic fracture |
| | | | 10070286 | Pubis fracture |
| | | | 10070884 | Atypical femur fracture |
| | | | 10072132 | Fracture pain |
| | | | 10072395 | Atypical fracture |
| | | | 10073162 | Chance fracture |
| | | | 10073853 | Osteochondral fracture |
| | | | 10074362 | Sacroiliac fracture |
| | | | 10074551 | Limb fracture |
| | | | 10074807 | Spinal fusion fracture |
| | | | 10077270 | Surgical fixation of rib fracture |
| | | | 10077603 | Craniofacial fracture |
| | | | 10078749 | Lisfranc fracture |
| | | | 10079667 | Metaphyseal corner fracture |
| | | | 10079813 | Fracture infection |
| | | | 10079864 | Subchondral insufficiency fracture |
| Narrow BIcMQ 'Diabetic ketoacidosis' | Events indicative of ketoacidosis (BIcMQ) | 40000008 | 10012668 | Diabetic hyperglycaemic coma |
| | | | 10012671 | Diabetic ketoacidosis |
| | | | 10012672 | Diabetic ketoacidotic hyperglycaemic coma |
| | | | 10023379 | Ketoacidosis |
| | | | 10080061 | Euglycaemic diabetic ketoacidosis |
| Narrow BIcMQ 'Genital tract infections predisposed to by glucosuria' | Genital infections (BIcMQ) | 40000004 | 10004055 | Bacterial vaginosis |
| | | | 10004074 | Balanitis candida |
| | | | 10004078 | Balanoposthitis |
| | | | 10004138 | Bartholin's abscess |
| | | | 10004142 | Bartholinitis |
| | | | 10008323 | Cervicitis |
| | | | 10014791 | Endometritis |
| | | | 10015000 | Epididymitis |
| | | | 10015001 | Epididymitis blastomyces |
| | | | 10018143 | Genital candidiasis |
| | | | 10018185 | Genitourinary chlamydia infection |
| | | | 10020497 | Hydrocele male infected |

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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Genital tract infections predisposed to by glucosuria' | Genital infections (BIcMQ) | 40000004 | | 10028885 | Necrotising fasciitis |
| | | | | 10030345 | Oophoritis |
| | | | | 10031064 | Orchitis |
| | | | | 10033119 | Ovarian abscess |
| | | | | 10033847 | Parametritis |
| | | | | 10034236 | Pelvic abscess |
| | | | | 10034254 | Pelvic inflammatory disease |
| | | | | 10034256 | Pelvic inflammatory disease mycoplasmal |
| | | | | 10034294 | Penile abscess |
| | | | | 10036934 | Prostatic abscess |
| | | | | 10036978 | Prostatitis |
| | | | | 10037651 | Pyometra |
| | | | | 10039453 | Salpingitis |
| | | | | 10039748 | Scrotal gangrene |
| | | | | 10039954 | Seminal vesiculitis |
| | | | | 10044250 | Toxic shock syndrome staphylococcal |
| | | | | 10044251 | Toxic shock syndrome streptococcal |
| | | | | 10046914 | Vaginal infection |
| | | | | 10046957 | Vaginitis gardnerella |
| | | | | 10047732 | Vulval abscess |
| | | | | 10047752 | Vulval cellulitis |
| | | | | 10047780 | Vulvitis |
| | | | | 10047784 | Vulvovaginal candidiasis |
| | | | | 10047794 | Vulvovaginitis |
| | | | | 10048461 | Genital infection |
| | | | | 10049205 | Clitoris abscess |
| | | | | 10049571 | Scrotal abscess |
| | | | | 10049573 | Vaginal abscess |
| | | | | 10049677 | Salpingo-oophoritis |
| | | | | 10050428 | Fallopian tube abscess |
| | | | | 10050662 | Prostate infection |
| | | | | 10050739 | Erosive balanitis |
| | | | | 10051458 | Myometritis |
| | | | | 10051483 | Prostatovesiculitis |
| | | | | 10052301 | Vaginal cellulitis |
| | | | | 10052457 | Perineal abscess |
| | | | | 10053043 | Epididymitis ureaplasmal |
| | | | | 10054259 | Escherichia vaginitis |
| | | | | 10054824 | Tubo-ovarian abscess |
| | | | | 10056254 | Intrauterine infection |
| | | | | 10056345 | Rectovaginal septum abscess |

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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Genital tract infections predisposed to by glucosuria' | Genital infections (BIcMQ) | 40000004 | | 10056628 | Ovarian bacterial infection |
| | | | | 10057001 | Seminal vesicular infection |
| | | | | 10058674 | Pelvic infection |
| | | | | 10059070 | Pelvic sepsis |
| | | | | 10061179 | Genital infection bacterial |
| | | | | 10061180 | Genital infection fungal |
| | | | | 10061182 | Genitourinary tract infection |
| | | | | 10061912 | Penile infection |
| | | | | 10061977 | Genital infection female |
| | | | | 10062156 | Scrotal infection |
| | | | | 10062233 | Uterine infection |
| | | | | 10062316 | Genital abscess |
| | | | | 10062521 | Genital infection male |
| | | | | 10062707 | Parametric abscess |
| | | | | 10063012 | Uterine abscess |
| | | | | 10064501 | Spermatic cord funiculitis |
| | | | | 10064724 | Testicular abscess |
| | | | | 10064899 | Vulvovaginal mycotic infection |
| | | | | 10064929 | Cellulitis of male external genital organ |
| | | | | 10066876 | Perineal infection |
| | | | | 10067185 | Vulvovaginitis streptococcal |
| | | | | 10067236 | Cervicitis streptococcal |
| | | | | 10067320 | Prostatitis Escherichia coli |
| | | | | 10067741 | Balanoposthitis infective |
| | | | | 10068682 | Gangrenous balanitis |
| | | | | 10069918 | Bacterial prostatitis |
| | | | | 10071209 | Candida cervicitis |
| | | | | 10072020 | Pyospermia |
| | | | | 10074861 | Endometritis bacterial |
| | | | | 10074997 | Mycoplasma genitalium infection |
| | | | | 10075062 | Cervicitis mycoplasmal |
| | | | | 10075620 | Seminal vesicle abscess |
| | | | | 10078662 | Bacterial salpingitis |
| | | | | 10079520 | Vulvovaginitis staphylococcal |
| | | | | 10079521 | Fungal balanitis |
| | | | | 10079528 | Bacterial vulvovaginitis |
| Narrow BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis' | Pyelonephritis or Urosepsis (BIcMQ) | 40000013 | | 10023424 | Kidney infection |
| | | | | 10034531 | Perinephric abscess |

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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis' | Pyelonephritis or Urosepsis (BIcMQ) | 40000013 | | 10037584 | Pyelitis |
| | | | | 10037596 | Pyelonephritis |
| | | | | 10037597 | Pyelonephritis acute |
| | | | | 10037601 | Pyelonephritis chronic |
| | | | | 10037603 | Pyelonephritis mycoplasmal |
| | | | | 10037653 | Pyonephrosis |
| | | | | 10038351 | Renal abscess |
| | | | | 10048709 | Urosepsis |
| | | | | 10049100 | Pyelocystitis |
| | | | | 10058596 | Renal cyst infection |
| | | | | 10059517 | Bacterial pyelonephritis |
| | | | | 10065214 | Pyelonephritis fungal |
| | | | | 10068822 | Emphysematous pyelonephritis |
| | | | | 10071736 | Acute focal bacterial nephritis |
| | | | | 10072058 | Perinephritis |
| | | | | 10074409 | Escherichia pyelonephritis |
| Narrow BIcMQ 'UTI predisposed by glucosuria' | Urinary tract infections (BIcMQ) | 40000002 | | 10004056 | Bacteriuria |
| | | | | 10004058 | Bacteriuria in pregnancy |
| | | | | 10011781 | Cystitis |
| | | | | 10011790 | Cystitis escherichia |
| | | | | 10011792 | Cystitis gonococcal |
| | | | | 10011793 | Cystitis haemorrhagic |
| | | | | 10011797 | Cystitis klebsiella |
| | | | | 10011799 | Cystitis pseudomonal |
| | | | | 10017525 | Fungal cystitis |
| | | | | 10023424 | Kidney infection |
| | | | | 10034531 | Perinephric abscess |
| | | | | 10037584 | Pyelitis |
| | | | | 10037596 | Pyelonephritis |
| | | | | 10037597 | Pyelonephritis acute |
| | | | | 10037601 | Pyelonephritis chronic |
| | | | | 10037603 | Pyelonephritis mycoplasmal |
| | | | | 10037653 | Pyonephrosis |
| | | | | 10038351 | Renal abscess |
| | | | | 10046424 | Urethral abscess |
| | | | | 10046470 | Urethral stricture post infection |
| | | | | 10046480 | Urethritis |
| | | | | 10046482 | Urethritis chlamydial |
| | | | | 10046483 | Urethritis gonococcal |

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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'UTI predisposed by glucosuria' | Urinary tract infections (BIcMQ) | 40000002 | | 10046489 | Urethritis trichomonal |
| | | | | 10046490 | Urethritis ureaplasmal |
| | | | | 10046571 | Urinary tract infection |
| | | | | 10046572 | Urinary tract infection enterococcal |
| | | | | 10046573 | Urinary tract infection neonatal |
| | | | | 10046704 | Urogenital trichomoniasis |
| | | | | 10048709 | Urosepsis |
| | | | | 10049059 | Urinary tract infection fungal |
| | | | | 10049100 | Pyelocystitis |
| | | | | 10050762 | Candiduria |
| | | | | 10051250 | Ureteritis |
| | | | | 10051959 | Urinary bladder abscess |
| | | | | 10052238 | Escherichia urinary tract infection |
| | | | | 10052299 | Urethral carbuncle |
| | | | | 10054088 | Urinary tract infection bacterial |
| | | | | 10056351 | Emphysematous cystitis |
| | | | | 10056396 | Asymptomatic bacteriuria |
| | | | | 10058523 | Bladder candidiasis |
| | | | | 10058596 | Renal cyst infection |
| | | | | 10059517 | Bacterial pyelonephritis |
| | | | | 10061181 | Genitourinary tract gonococcal infection |
| | | | | 10061395 | Ureter abscess |
| | | | | 10062279 | Urinary tract infection pseudomonal |
| | | | | 10062280 | Urinary tract infection staphylococcal |
| | | | | 10064850 | Cystitis erosive |
| | | | | 10065198 | Cystitis bacterial |
| | | | | 10065214 | Pyelonephritis fungal |
| | | | | 10065582 | Urogenital infection fungal |
| | | | | 10065583 | Urogenital infection bacterial |
| | | | | 10066757 | Urinary tract abscess |
| | | | | 10068822 | Emphysematous pyelonephritis |
| | | | | 10070300 | Streptococcal urinary tract infection |
| | | | | 10071736 | Acute focal bacterial nephritis |
| | | | | 10072058 | Perinephritis |
| | | | | 10074409 | Escherichia pyelonephritis |
| | | | | 10074457 | Bladder diverticulitis |
| | | | | 10075063 | Urethritis mycoplasmal |
| | | | | 10077375 | Funguria |
| | | | | 10078665 | Bacterial urethritis |
| | | | | 10078666 | Bacterial ureteritis |

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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code Scope | Preferred term code | Preferred term |
|---|---|---|---|---|
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration' | Volume depletion events (BIcMQ) | 40000006 | 10005731 | Blood pressure ambulatory decreased |
| | | | 10005734 | Blood pressure decreased |
| | | | 10005737 | Blood pressure diastolic decreased |
| | | | 10005758 | Blood pressure systolic decreased |
| | | | 10009192 | Circulatory collapse |
| | | | 10012174 | Dehydration |
| | | | 10021097 | Hypotension |
| | | | 10021137 | Hypovolaemia |
| | | | 10021138 | Hypovolaemic shock |
| | | | 10026983 | Mean arterial pressure decreased |
| | | | 10031127 | Orthostatic hypotension |
| | | | 10036653 | Presyncope |
| | | | 10042772 | Syncope |
| | | | 10053356 | Blood pressure orthostatic decreased |
| | | | 10066077 | Diastolic hypotension |
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration' excluding PTs 'Dehydration' and 'Hypovolaemia' | Hypotension events (BIcMQ) | 40000001 | 10005731 | Blood pressure ambulatory decreased |
| | | | 10005734 | Blood pressure decreased |
| | | | 10005737 | Blood pressure diastolic decreased |
| | | | 10005758 | Blood pressure systolic decreased |
| | | | 10009192 | Circulatory collapse |
| | | | 10021097 | Hypotension |
| | | | 10021138 | Hypovolaemic shock |
| | | | 10026983 | Mean arterial pressure decreased |
| | | | 10031127 | Orthostatic hypotension |
| | | | 10036653 | Presyncope |
| | | | 10042772 | Syncope |
| | | | 10053356 | Blood pressure orthostatic decreased |
| | | | 10066077 | Diastolic hypotension |
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | 10000804 | Acute hepatic failure |
| | | | 10001547 | Alanine aminotransferase abnormal |
| | | | 10001551 | Alanine aminotransferase increased |
| | | | 10001942 | Ammonia abnormal |

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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10001946 | Ammonia increased |
| | | | | 10003445 | Ascites |
| | | | | 10003477 | Aspartate aminotransferase abnormal |
| | | | | 10003481 | Aspartate aminotransferase increased |
| | | | | 10003547 | Asterixis |
| | | | | 10003827 | Autoimmune hepatitis |
| | | | | 10004659 | Biliary cirrhosis |
| | | | | 10004661 | Biliary cirrhosis primary |
| | | | | 10004664 | Biliary fibrosis |
| | | | | 10004685 | Bilirubin conjugated increased |
| | | | | 10004792 | Biopsy liver abnormal |
| | | | | 10005364 | Blood bilirubin increased |
| | | | | 10005370 | Blood bilirubin unconjugated increased |
| | | | | 10006408 | Bromosulphthalein test abnormal |
| | | | | 10008635 | Cholestasis |
| | | | | 10008909 | Chronic hepatitis |
| | | | | 10010075 | Coma hepatic |
| | | | | 10017688 | Gamma-glutamyltransferase abnormal |
| | | | | 10017693 | Gamma-glutamyltransferase increased |
| | | | | 10019621 | Hepaplastin abnormal |
| | | | | 10019622 | Hepaplastin decreased |
| | | | | 10019637 | Hepatic atrophy |
| | | | | 10019641 | Hepatic cirrhosis |
| | | | | 10019645 | Hepatic congestion |
| | | | | 10019660 | Hepatic encephalopathy |
| | | | | 10019663 | Hepatic failure |
| | | | | 10019668 | Hepatic fibrosis |
| | | | | 10019670 | Hepatic function abnormal |
| | | | | 10019692 | Hepatic necrosis |
| | | | | 10019705 | Hepatic pain |
| | | | | 10019708 | Hepatic steatosis |
| | | | | 10019717 | Hepatitis |
| | | | | 10019727 | Hepatitis acute |
| | | | | 10019754 | Hepatitis cholestatic |
| | | | | 10019755 | Hepatitis chronic active |
| | | | | 10019759 | Hepatitis chronic persistent |
| | | | | 10019772 | Hepatitis fulminant |

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Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10019795 | Hepatitis toxic |
| | | | | 10019837 | Hepatocellular injury |
| | | | | 10019842 | Hepatomegaly |
| | | | | 10019845 | Hepatorenal failure |
| | | | | 10019846 | Hepatorenal syndrome |
| | | | | 10019847 | Hepatosplenomegaly |
| | | | | 10019851 | Hepatotoxicity |
| | | | | 10020575 | Hyperammonaemia |
| | | | | 10020578 | Hyperbilirubinaemia |
| | | | | 10021209 | Icterus index increased |
| | | | | 10023025 | Ischaemic hepatitis |
| | | | | 10023126 | Jaundice |
| | | | | 10023129 | Jaundice cholestatic |
| | | | | 10023136 | Jaundice hepatocellular |
| | | | | 10023321 | Kayser-Fleischer ring |
| | | | | 10024670 | Liver disorder |
| | | | | 10024690 | Liver function test abnormal |
| | | | | 10024712 | Liver tenderness |
| | | | | 10024714 | Liver transplant |
| | | | | 10025129 | Lupoid hepatic cirrhosis |
| | | | | 10029530 | Non-alcoholic fatty liver |
| | | | | 10030210 | Oesophageal varices haemorrhage |
| | | | | 10036200 | Portal hypertension |
| | | | | 10039012 | Reye's syndrome |
| | | | | 10045428 | Ultrasound liver abnormal |
| | | | | 10048611 | Cholaemia |
| | | | | 10049631 | Oedema due to hepatic disease |
| | | | | 10050792 | Urine bilirubin increased |
| | | | | 10050897 | Portal hypertensive gastropathy |
| | | | | 10051010 | Duodenal varices |
| | | | | 10051012 | Gastric varices |
| | | | | 10051015 | Radiation hepatitis |
| | | | | 10051081 | Nodular regenerative hyperplasia |
| | | | | 10051333 | Guanase increased |
| | | | | 10051343 | Bile output decreased |
| | | | | 10051344 | Bile output abnormal |
| | | | | 10051924 | Hypercholia |

Analyses are based on 1245.137.
MedDRA version: 20.1

Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10052274 | Hepatopulmonary syndrome |
| | | | | 10052279 | Renal and liver transplant |
| | | | | 10052280 | Liver and small intestine transplant |
| | | | | 10052550 | Liver induration |
| | | | | 10052554 | Foetor hepaticus |
| | | | | 10053219 | Non-alcoholic steatohepatitis |
| | | | | 10053244 | Hepatocellular foamy cell syndrome |
| | | | | 10054125 | Perihepatic discomfort |
| | | | | 10054889 | Transaminases increased |
| | | | | 10056091 | Varices oesophageal |
| | | | | 10056536 | X-ray hepatobiliary abnormal |
| | | | | 10056956 | Subacute hepatic failure |
| | | | | 10057110 | Hepatic mass |
| | | | | 10057572 | Gastric varices haemorrhage |
| | | | | 10057573 | Chronic hepatic failure |
| | | | | 10058117 | Ocular icterus |
| | | | | 10058477 | Blood bilirubin abnormal |
| | | | | 10059710 | Galactose elimination capacity test abnormal |
| | | | | 10059712 | Galactose elimination capacity test decreased |
| | | | | 10060794 | Hepatic enzyme decreased |
| | | | | 10060795 | Hepatic enzyme increased |
| | | | | 10061009 | Bilirubin excretion disorder |
| | | | | 10061947 | Liver scan abnormal |
| | | | | 10061997 | Hepatectomy |
| | | | | 10061998 | Hepatic lesion |
| | | | | 10062000 | Hepatobiliary disease |
| | | | | 10062040 | Liver operation |
| | | | | 10062685 | Hepatic enzyme abnormal |
| | | | | 10062688 | Transaminases abnormal |
| | | | | 10063075 | Cryptogenic cirrhosis |
| | | | | 10064190 | Cholestatic pruritus |
| | | | | 10064558 | Total bile acids increased |
| | | | | 10064668 | Hepatic infiltration eosinophilic |
| | | | | 10064676 | Graft versus host disease in liver |

Analyses are based on 1245.137.
MedDRA version: 20.1

Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10064712 | Mitochondrial aspartate aminotransferase increased |
| | | | | 10065274 | Hepatic calcification |
| | | | | 10066195 | Hepatobiliary scan abnormal |
| | | | | 10066244 | Hepatic sequestration |
| | | | | 10066263 | Acute graft versus host disease in liver |
| | | | | 10066599 | Hepatic encephalopathy prophylaxis |
| | | | | 10066758 | Mixed liver injury |
| | | | | 10066869 | Molar ratio of total branched-chain amino acid to tyrosine |
| | | | | 10067125 | Liver injury |
| | | | | 10067281 | Portopulmonary hypertension |
| | | | | 10067338 | Retrograde portal vein flow |
| | | | | 10067365 | Hepatic hydrothorax |
| | | | | 10067718 | Bilirubin conjugated abnormal |
| | | | | 10067737 | Lupus hepatitis |
| | | | | 10067823 | Splenic varices |
| | | | | 10067969 | Cholestatic liver injury |
| | | | | 10068237 | Hypertransaminasaemia |
| | | | | 10068287 | Child-Pugh-Turcotte score increased |
| | | | | 10068358 | Hepatic vascular resistance increased |
| | | | | 10068547 | Bacterascites |
| | | | | 10068662 | Splenic varices haemorrhage |
| | | | | 10068923 | Portal hypertensive enteropathy |
| | | | | 10068997 | Hepatic artery flow decreased |
| | | | | 10070815 | Acute yellow liver atrophy |
| | | | | 10070953 | Reynold's syndrome |
| | | | | 10071198 | Allergic hepatitis |
| | | | | 10071265 | Diabetic hepatopathy |
| | | | | 10071502 | Intestinal varices |
| | | | | 10072160 | Chronic graft versus host disease in liver |
| | | | | 10072268 | Drug-induced liver injury |
| | | | | 10072284 | Varicose veins of abdominal wall |
| | | | | 10072319 | Gallbladder varices |
| | | | | 10073209 | Portal vein dilatation |
| | | | | 10073215 | Peripancreatic varices |
| | | | | 10073979 | Portal vein cavernous transformation |

Analyses are based on 1245.137.
MedDRA version: 20.1

Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10074150 | Biliary ascites |
| | | | | 10074151 | Parenteral nutrition associated liver disease |
| | | | | 10074726 | Portal fibrosis |
| | | | | 10075895 | Liver palpable |
| | | | | 10076204 | Minimal hepatic encephalopathy |
| | | | | 10076215 | Computerised tomogram liver |
| | | | | 10076237 | Gastric variceal injection |
| | | | | 10076238 | Gastric variceal ligation |
| | | | | 10076254 | Hepatic hypertrophy |
| | | | | 10076331 | Steatohepatitis |
| | | | | 10076640 | Liver dialysis |
| | | | | 10077020 | Child-Pugh-Turcotte score abnormal |
| | | | | 10077215 | Hepatic steato-fibrosis |
| | | | | 10077259 | Non-cirrhotic portal hypertension |
| | | | | 10077305 | Acute on chronic liver failure |
| | | | | 10077356 | Bilirubin urine present |
| | | | | 10077677 | Liver function test decreased |
| | | | | 10077692 | Liver function test increased |
| | | | | 10078058 | Intestinal varices haemorrhage |
| | | | | 10078360 | Computerised tomogram liver abnormal |
| | | | | 10078438 | White nipple sign |
| | | | | 10079446 | Portal hypertensive colopathy |
| | | | | 10080035 | Nuclear magnetic resonance imaging liver abnormal |
| SMQ 'Acute renal failure' | Acute renal failure (SMQ) | 20000003 | Narrow | 10001017 | Acute prerenal failure |
| | | | | 10002847 | Anuria |
| | | | | 10003885 | Azotaemia |
| | | | | 10018875 | Haemodialysis |
| | | | | 10029155 | Nephropathy toxic |
| | | | | 10030302 | Oliguria |
| | | | | 10034660 | Peritoneal dialysis |
| | | | | 10038435 | Renal failure |
| | | | | 10038447 | Renal failure neonatal |
| | | | | 10049776 | Renal impairment neonatal |

Analyses are based on 1245.137.
MedDRA version: 20.1

Listing R.1.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ or SMQs

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| SMQ 'Acute renal failure' | Acute renal failure (SMQ) | 20000003 | Narrow | 10049778 | Neonatal anuria |
| | | | | 10053090 | Haemofiltration |
| | | | | 10061105 | Dialysis |
| | | | | 10062237 | Renal impairment |
| | | | | 10066338 | Continuous haemodiafiltration |
| | | | | 10069339 | Acute kidney injury |
| | | | | 10069688 | Acute phosphate nephropathy |
| | | | | 10072370 | Prerenal failure |
| | | | | 10077515 | Hyponatriuria |
| | | | | 10078987 | Foetal renal impairment |
| SMQ 'Hypoglycaemia' | Hypoglycaemic events (SMQ) | 20000226 | Narrow | 10005555 | Blood glucose decreased |
| | | | | 10020993 | Hypoglycaemia |
| | | | | 10020994 | Hypoglycaemia neonatal |
| | | | | 10020997 | Hypoglycaemia unawareness |
| | | | | 10021000 | Hypoglycaemic coma |
| | | | | 10021002 | Hypoglycaemic encephalopathy |
| | | | | 10040576 | Shock hypoglycaemic |
| | | | | 10048803 | Hypoglycaemic seizure |
| | | | | 10054998 | Neuroglycopenia |
| | | | | 10059035 | Postprandial hypoglycaemia |
| | | | | 10065981 | Hypoglycaemic unconsciousness |
| | | | | 10077216 | Hyperinsulinaemic hypoglycaemia |
| | | | | 10080024 | Nesidioblastosis |

Analyses are based on 1245.137.
MedDRA version: 20.1

Listing R.1.2.6: 2 Preferred terms that define adverse events of special interest and other specific AE categories for adjudication events or events defined via user-defined searches

| Group | Group code | Preferred term code | Preferred term |
|---|---|---|---|
| Gout | GOUT | 10018627 | Gout |
| | | 10018634 | Gouty arthritis |
| | | 10018641 | Gouty tophus |
| Hyperkalaemia | HKAL | 10005725 | Blood potassium increased |
| | | 10020646 | Hyperkalaemia |
| Lower limb amputation | AMPUT | 10016960 | Foot amputation |
| | | 10043913 | Toe amputation |
| | | 1100069* | Forefoot amputation |
| | | 1100070* | Below-knee amputation |
| | | 1100071* | Above-knee amputation |
| Symptomatic dehydration | DEHYD | 10012174 | Dehydration |
| | | 10021137 | Hypovolaemia |

Analyses are based on 1245.137.
MedDRA version: 20.1
* Extra term.

**R.2**

**R.2.1**

**R.2.1.1**

**R.2.1.1.1**

R.2.1.1.1.1 Time to all-cause mortality

Table R.2.1.1.1.1: 1 Cox Regression for time to all-cause mortality until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 343 | 17.1 | 8.09 | 2053 | 344 | 16.8 | 7.96 | 1.00 | (0.86,1.16) | 0.9861 | |
| Sex | | | | | | | | | | | | 0.9519 |
| Male | 1065 | 209 | 19.6 | 9.34 | 1094 | 211 | 19.3 | 9.18 | 1.01 | (0.83,1.22) | 0.9591 | |
| Female | 938 | 134 | 14.3 | 6.70 | 959 | 133 | 13.9 | 6.56 | 1.00 | (0.78,1.27) | 0.9711 | |
| Age [years] | | | | | | | | | | | | 0.9944 |
| <65 | 331 | 48 | 14.5 | 6.69 | 313 | 44 | 14.1 | 6.65 | 1.00 | (0.66,1.50) | 0.9827 | |
| >=65 | 1672 | 295 | 17.6 | 8.38 | 1740 | 300 | 17.2 | 8.19 | 1.00 | (0.85,1.17) | 0.9713 | |
| Region | | | | | | | | | | | | 0.5568 |
| North America | 273 | 40 | 14.7 | 6.41 | 274 | 47 | 17.2 | 7.72 | 1.14 | (0.75,1.74) | 0.5418 | |
| Latin America | 511 | 113 | 22.1 | 11.20 | 504 | 111 | 22.0 | 11.21 | 1.02 | (0.79,1.33) | 0.8689 | |
| Europe | 867 | 139 | 16.0 | 7.47 | 894 | 136 | 15.2 | 7.12 | 0.97 | (0.76,1.23) | 0.7833 | |
| Asia | 231 | 28 | 12.1 | 5.65 | 248 | 21 | 8.5 | 3.84 | 0.68 | (0.39,1.20) | 0.1816 | |
| Other | 121 | 23 | 19.0 | 9.12 | 133 | 29 | 21.8 | 10.85 | 1.27 | (0.74,2.20) | 0.3873 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9249 |
| Diabetic | 1046 | 192 | 18.4 | 8.61 | 1082 | 193 | 17.8 | 8.48 | 0.99 | (0.81,1.21) | 0.9551 | |
| Non-Diabetic | 957 | 151 | 15.8 | 7.51 | 971 | 151 | 15.6 | 7.37 | 1.01 | (0.80,1.26) | 0.9393 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1552 |
| <30 | 1087 | 213 | 19.6 | 9.51 | 1094 | 192 | 17.6 | 8.42 | 0.92 | (0.75,1.11) | 0.3796 | |
| >=30 | 916 | 130 | 14.2 | 6.50 | 959 | 152 | 15.8 | 7.44 | 1.14 | (0.90,1.44) | 0.2634 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5589 |
| <130 | 827 | 134 | 16.2 | 7.76 | 853 | 142 | 16.6 | 7.96 | 1.06 | (0.83,1.34) | 0.6422 | |
| >=130 | 1176 | 209 | 17.8 | 8.31 | 1200 | 202 | 16.8 | 7.95 | 0.97 | (0.80,1.17) | 0.7213 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7730 |
| <75 | 936 | 170 | 18.2 | 8.60 | 935 | 157 | 16.8 | 7.98 | 0.95 | (0.76,1.18) | 0.6274 | |
| 75 to <85 | 658 | 108 | 16.4 | 7.71 | 703 | 119 | 16.9 | 8.09 | 1.07 | (0.82,1.39) | 0.6127 | |
| >=85 | 409 | 65 | 15.9 | 7.54 | 415 | 68 | 16.4 | 7.68 | 1.03 | (0.73,1.44) | 0.8753 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.2.1.1.1.1: 1 Cox Regression for time to all-cause mortality until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1683 |
| <30 | 161 | 56 | 34.8 | 18.24 | 148 | 37 | 25.0 | 12.38 | 0.71 | (0.47,1.08) | 0.1064 | |
| 30 to <45 | 550 | 89 | 16.2 | 7.59 | 564 | 97 | 17.2 | 8.22 | 1.15 | (0.86,1.54) | 0.3346 | |
| >=45 | 1291 | 198 | 15.3 | 7.18 | 1341 | 210 | 15.7 | 7.38 | 1.02 | (0.84,1.24) | 0.8578 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4770 |
| Normal (<30) | 766 | 93 | 12.1 | 5.68 | 787 | 108 | 13.7 | 6.48 | 1.16 | (0.88,1.53) | 0.2941 | |
| Microalbuminuria (30 to <=300) | 921 | 171 | 18.6 | 8.84 | 939 | 162 | 17.3 | 8.14 | 0.93 | (0.75,1.16) | 0.5279 | |
| Macroalbuminuria (>300) | 311 | 79 | 25.4 | 12.08 | 318 | 74 | 23.3 | 11.43 | 1.00 | (0.73,1.37) | 0.9950 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.9763 |
| Low, moderate or high | 1479 | 213 | 14.4 | 6.74 | 1549 | 225 | 14.5 | 6.81 | 1.01 | (0.84,1.22) | 0.8789 | |
| Very high | 519 | 130 | 25.0 | 12.19 | 495 | 119 | 24.0 | 11.88 | 1.02 | (0.79,1.31) | 0.8795 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.4242 |
| No | 412 | 78 | 18.9 | 9.05 | 411 | 71 | 17.3 | 8.11 | 0.89 | (0.65,1.23) | 0.4832 | |
| Yes | 1591 | 265 | 16.7 | 7.84 | 1642 | 273 | 16.6 | 7.92 | 1.03 | (0.87,1.22) | 0.7011 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5120 |
| No | 282 | 65 | 23.0 | 11.12 | 277 | 52 | 18.8 | 9.29 | 0.90 | (0.62,1.30) | 0.5720 | |
| Yes | 1721 | 278 | 16.2 | 7.61 | 1776 | 292 | 16.4 | 7.76 | 1.03 | (0.87,1.21) | 0.7317 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.4444 |
| No | 229 | 36 | 15.7 | 7.30 | 250 | 30 | 12.0 | 5.75 | 0.84 | (0.51,1.36) | 0.4696 | |
| Yes | 1774 | 307 | 17.3 | 8.19 | 1803 | 314 | 17.4 | 8.26 | 1.02 | (0.87,1.19) | 0.8024 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.1.1: 1**

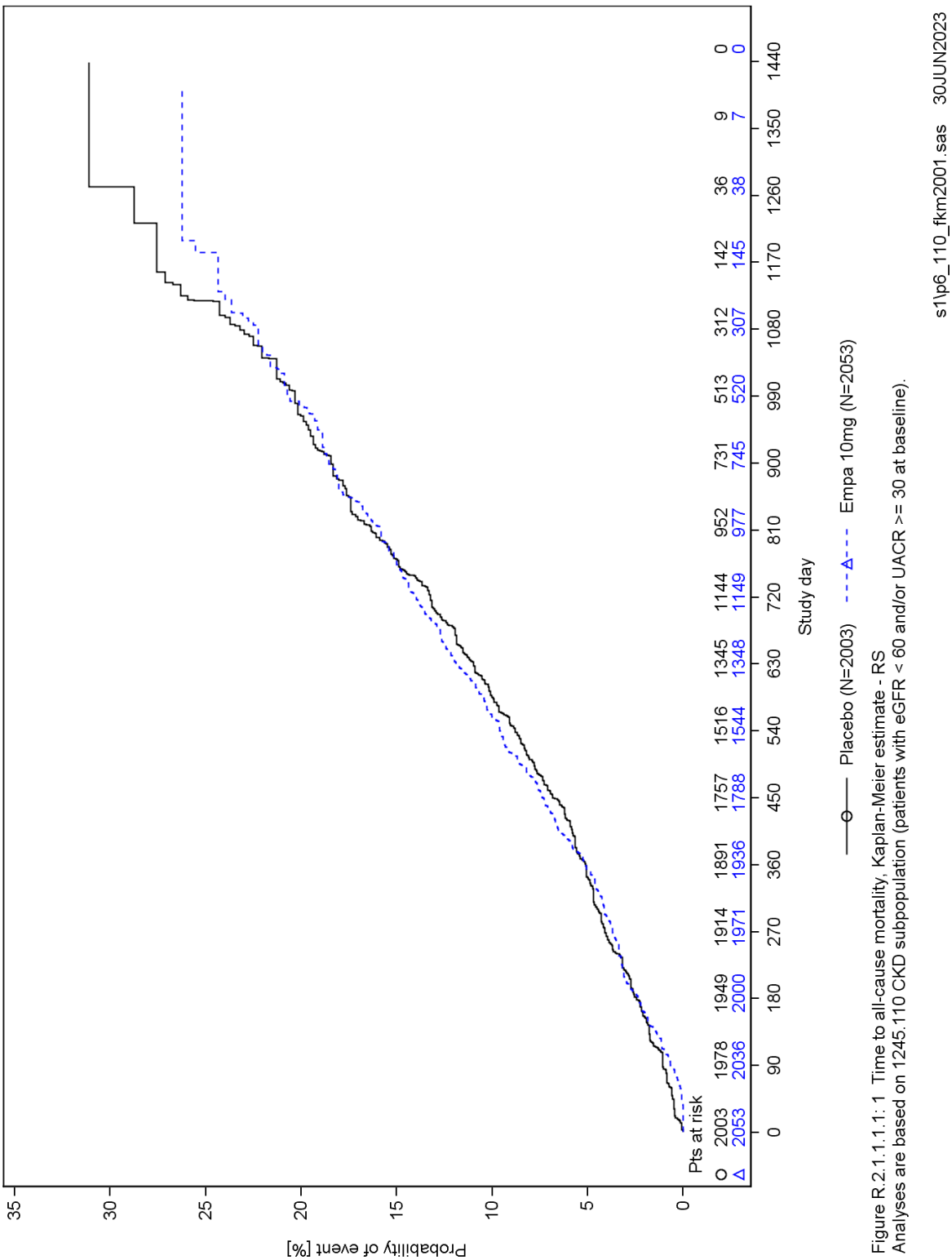


Figure R.2.1.1.1.1: 1 Time to all-cause mortality, Kaplan-Meier estimate - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.2.1.1.1.2**

R.2.1.1.1.2 Time to adjudicated CV death

Table R.2.1.1.1.2: 1 Cox Regression for time to adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2003 | 199 | 9.9 | 4.69 | 2053 | 185 | 9.0 | 4.28 | 0.93 | (0.76,1.13) | 0.4592 | |
| Sex | | | | | | | | | | | | 0.6799 |
| Male | 1065 | 117 | 11.0 | 5.23 | 1094 | 113 | 10.3 | 4.92 | 0.96 | (0.74,1.24) | 0.7553 | |
| Female | 938 | 82 | 8.7 | 4.10 | 959 | 72 | 7.5 | 3.55 | 0.88 | (0.64,1.21) | 0.4311 | |
| Age [years] | | | | | | | | | | | | 0.3507 |
| <65 | 331 | 24 | 7.3 | 3.34 | 313 | 26 | 8.3 | 3.93 | 1.18 | (0.68,2.06) | 0.5552 | |
| >=65 | 1672 | 175 | 10.5 | 4.97 | 1740 | 159 | 9.1 | 4.34 | 0.89 | (0.72,1.10) | 0.2887 | |
| Region | | | | | | | | | | | | 0.2437 |
| North America | 273 | 21 | 7.7 | 3.36 | 274 | 26 | 9.5 | 4.27 | 1.21 | (0.68,2.16) | 0.5072 | |
| Latin America | 511 | 62 | 12.1 | 6.15 | 504 | 64 | 12.7 | 6.46 | 1.07 | (0.75,1.51) | 0.7124 | |
| Europe | 867 | 88 | 10.1 | 4.73 | 894 | 68 | 7.6 | 3.56 | 0.77 | (0.56,1.05) | 0.1001 | |
| Asia | 231 | 18 | 7.8 | 3.63 | 248 | 12 | 4.8 | 2.20 | 0.61 | (0.29,1.26) | 0.1799 | |
| Other | 121 | 10 | 8.3 | 3.97 | 133 | 15 | 11.3 | 5.61 | 1.48 | (0.66,3.29) | 0.3391 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.6071 |
| Diabetic | 1046 | 106 | 10.1 | 4.75 | 1082 | 104 | 9.6 | 4.57 | 0.97 | (0.74,1.27) | 0.8344 | |
| Non-Diabetic | 957 | 93 | 9.7 | 4.63 | 971 | 81 | 8.3 | 3.96 | 0.87 | (0.65,1.18) | 0.3764 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2509 |
| <30 | 1087 | 126 | 11.6 | 5.63 | 1094 | 105 | 9.6 | 4.60 | 0.84 | (0.65,1.09) | 0.2006 | |
| >=30 | 916 | 73 | 8.0 | 3.65 | 959 | 80 | 8.3 | 3.92 | 1.07 | (0.78,1.47) | 0.6617 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7874 |
| <130 | 827 | 74 | 8.9 | 4.29 | 853 | 72 | 8.4 | 4.04 | 0.96 | (0.69,1.33) | 0.8113 | |
| >=130 | 1176 | 125 | 10.6 | 4.97 | 1200 | 113 | 9.4 | 4.45 | 0.91 | (0.70,1.17) | 0.4579 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5624 |
| <75 | 936 | 96 | 10.3 | 4.85 | 935 | 92 | 9.8 | 4.68 | 0.98 | (0.74,1.31) | 0.9108 | |
| 75 to <85 | 658 | 70 | 10.6 | 5.00 | 703 | 58 | 8.3 | 3.94 | 0.80 | (0.56,1.13) | 0.2034 | |
| >=85 | 409 | 33 | 8.1 | 3.83 | 415 | 35 | 8.4 | 3.95 | 1.05 | (0.65,1.69) | 0.8345 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.2.1.1.1.2: 1 Cox Regression for time to adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1481 |
| <30 | 161 | 26 | 16.1 | 8.47 | 148 | 17 | 11.5 | 5.69 | 0.73 | (0.39,1.34) | 0.3103 | |
| 30 to <45 | 550 | 43 | 7.8 | 3.67 | 564 | 54 | 9.6 | 4.58 | 1.30 | (0.87,1.94) | 0.1986 | |
| >=45 | 1291 | 130 | 10.1 | 4.71 | 1341 | 114 | 8.5 | 4.01 | 0.85 | (0.66,1.09) | 0.1972 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.6785 |
| Normal (<30) | 766 | 55 | 7.2 | 3.36 | 787 | 54 | 6.9 | 3.24 | 0.97 | (0.67,1.42) | 0.8941 | |
| Microalbuminuria (30 to <=300) | 921 | 102 | 11.1 | 5.27 | 939 | 89 | 9.5 | 4.47 | 0.86 | (0.65,1.14) | 0.3018 | |
| Macroalbuminuria (>300) | 311 | 42 | 13.5 | 6.42 | 318 | 42 | 13.2 | 6.49 | 1.07 | (0.70,1.65) | 0.7414 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2195 |
| Low, moderate or high | 1479 | 133 | 9.0 | 4.21 | 1549 | 119 | 7.7 | 3.60 | 0.86 | (0.67,1.10) | 0.2316 | |
| Very high | 519 | 66 | 12.7 | 6.19 | 495 | 66 | 13.3 | 6.59 | 1.12 | (0.80,1.58) | 0.5150 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7606 |
| No | 412 | 40 | 9.7 | 4.64 | 411 | 40 | 9.7 | 4.57 | 0.99 | (0.64,1.53) | 0.9462 | |
| Yes | 1591 | 159 | 10.0 | 4.71 | 1642 | 145 | 8.8 | 4.21 | 0.91 | (0.73,1.14) | 0.4245 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3627 |
| No | 282 | 30 | 10.6 | 5.13 | 277 | 31 | 11.2 | 5.54 | 1.15 | (0.70,1.91) | 0.5796 | |
| Yes | 1721 | 169 | 9.8 | 4.62 | 1776 | 154 | 8.7 | 4.09 | 0.89 | (0.72,1.11) | 0.3121 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2792 |
| No | 229 | 25 | 10.9 | 5.07 | 250 | 17 | 6.8 | 3.26 | 0.67 | (0.36,1.25) | 0.2072 | |
| Yes | 1774 | 174 | 9.8 | 4.64 | 1803 | 168 | 9.3 | 4.42 | 0.96 | (0.78,1.19) | 0.7347 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.1.2: 1**

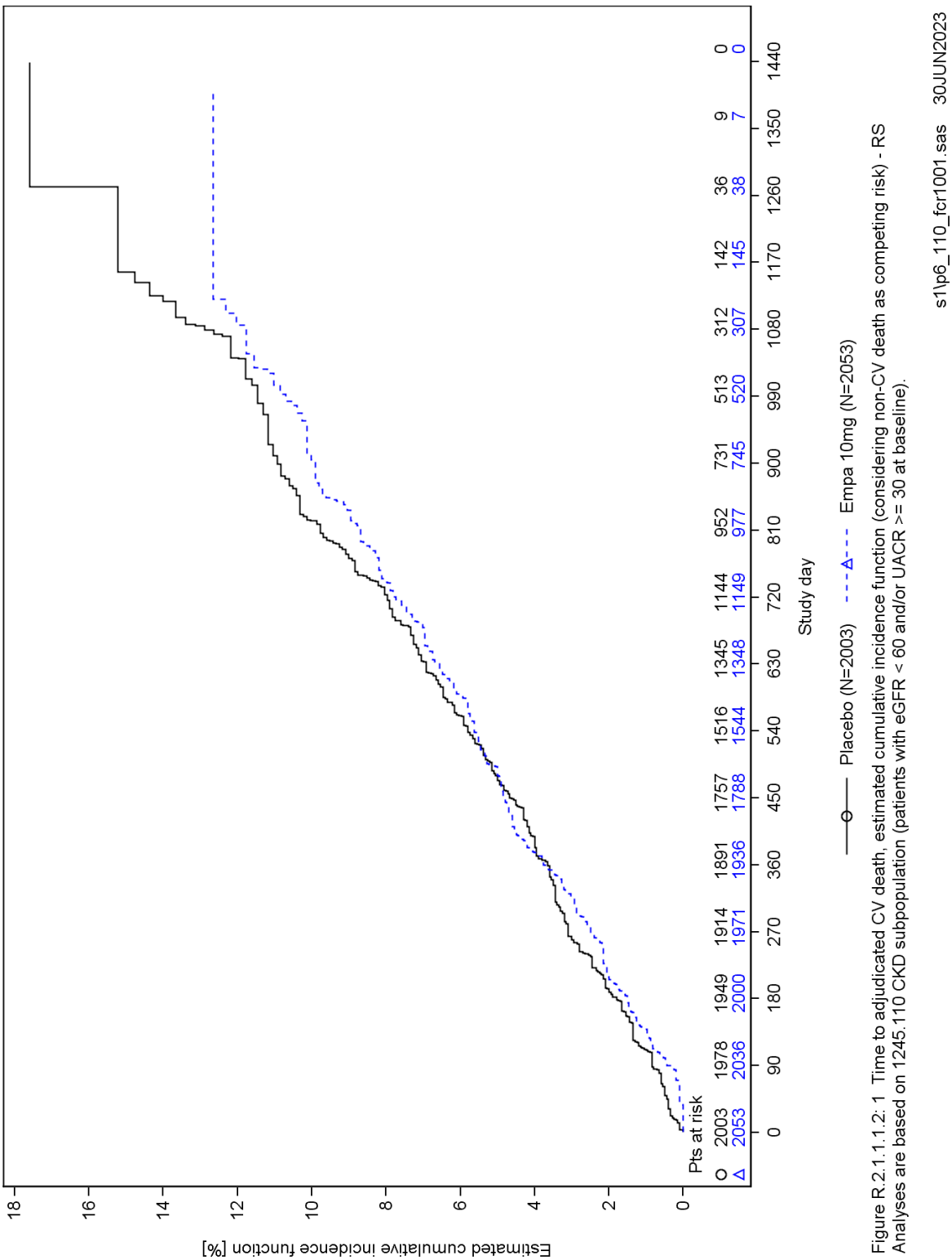


Figure R.2.1.1.1.2: 1 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.2.1.1.1.3**

R.2.1.1.1.3 Time to adjudicated renal death

Table R.2.1.1.1.3: 1 Cox Regression for time to adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 10 | 0.5 | 0.24 | 2053 | 3 | 0.1 | 0.07 | 0.28 | (0.08, 1.05) | 0.0591 | |
| Sex | | | | | | | | | | | | 0.2779 |
| Male | 1065 | 9 | 0.8 | 0.40 | 1094 | 2 | 0.2 | 0.09 | 0.20 | (0.04, 0.95) | 0.0428 | |
| Female | 938 | 1 | 0.1 | 0.05 | 959 | 1 | 0.1 | 0.05 | 1.17 | (0.07,18.83) | 0.9110 | |
| Age [years] | | | | | | | | | | | | |
| <65 | 331 | 5 | 1.5 | 0.70 | 313 | 3 | 1.0 | 0.45 | | | | |
| >=65 | 1672 | 5 | 0.3 | 0.14 | 1740 | 0 | 0 | 0.00 | | | | |
| Region | | | | | | | | | | | | |
| North America | 273 | 2 | 0.7 | 0.32 | 274 | 1 | 0.4 | 0.16 | | | | |
| Latin America | 511 | 4 | 0.8 | 0.40 | 504 | 1 | 0.2 | 0.10 | | | | |
| Europe | 867 | 0 | 0 | 0.00 | 894 | 0 | 0 | 0.00 | | | | |
| Asia | 231 | 1 | 0.4 | 0.20 | 248 | 0 | 0 | 0.00 | | | | |
| Other | 121 | 3 | 2.5 | 1.19 | 133 | 1 | 0.8 | 0.37 | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9903 |
| Diabetic | 1046 | 7 | 0.7 | 0.31 | 1082 | 3 | 0.3 | 0.13 | 0.43 | (0.11, 1.67) | 0.2204 | |
| Non-Diabetic | 957 | 3 | 0.3 | 0.15 | 971 | 0 | 0 | 0.00 | <0.01 | | 0.9897 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | |
| <30 | 1087 | 6 | 0.6 | 0.27 | 1094 | 1 | 0.1 | 0.04 | | | | |
| >=30 | 916 | 4 | 0.4 | 0.20 | 959 | 2 | 0.2 | 0.10 | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 827 | 7 | 0.8 | 0.41 | 853 | 1 | 0.1 | 0.06 | | | | |
| >=130 | 1176 | 3 | 0.3 | 0.12 | 1200 | 2 | 0.2 | 0.08 | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 936 | 5 | 0.5 | 0.25 | 935 | 1 | 0.1 | 0.05 | | | | |
| 75 to <85 | 658 | 2 | 0.3 | 0.14 | 703 | 0 | 0 | 0.00 | | | | |
| >=85 | 409 | 3 | 0.7 | 0.35 | 415 | 2 | 0.5 | 0.23 | | | | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.2.1.1.1.3: 1 Cox Regression for time to adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 161 | 4 | 2.5 | 1.30 | 148 | 0 | 0 | 0.00 | | | | |
| 30 to <45 | 550 | 5 | 0.9 | 0.43 | 564 | 2 | 0.4 | 0.17 | | | | |
| >=45 | 1291 | 1 | 0.1 | 0.04 | 1341 | 1 | 0.1 | 0.04 | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 766 | 1 | 0.1 | 0.06 | 787 | 1 | 0.1 | 0.06 | | | | |
| Microalbuminuria (30 to <=300) | 921 | 4 | 0.4 | 0.21 | 939 | 0 | 0 | 0.00 | | | | |
| Macroalbuminuria (>300) | 311 | 5 | 1.6 | 0.76 | 318 | 2 | 0.6 | 0.31 | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | |
| Low, moderate or high | 1479 | 2 | 0.1 | 0.06 | 1549 | 2 | 0.1 | 0.06 | | | | |
| Very high | 519 | 8 | 1.5 | 0.75 | 495 | 1 | 0.2 | 0.10 | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | |
| No | 412 | 4 | 1.0 | 0.46 | 411 | 0 | 0 | 0.00 | | | | |
| Yes | 1591 | 6 | 0.4 | 0.18 | 1642 | 3 | 0.2 | 0.09 | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.7077 |
| No | 282 | 2 | 0.7 | 0.34 | 277 | 1 | 0.4 | 0.18 | 0.42 | (0.04, 4.86) | 0.4864 | |
| Yes | 1721 | 8 | 0.5 | 0.22 | 1776 | 2 | 0.1 | 0.05 | 0.24 | (0.05, 1.15) | 0.0745 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9969 |
| No | 229 | 1 | 0.4 | 0.20 | 250 | 0 | 0 | 0.00 | <0.01 | | 0.9967 | |
| Yes | 1774 | 9 | 0.5 | 0.24 | 1803 | 3 | 0.2 | 0.08 | 0.33 | (0.09, 1.23) | 0.0984 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.1.3: 1**

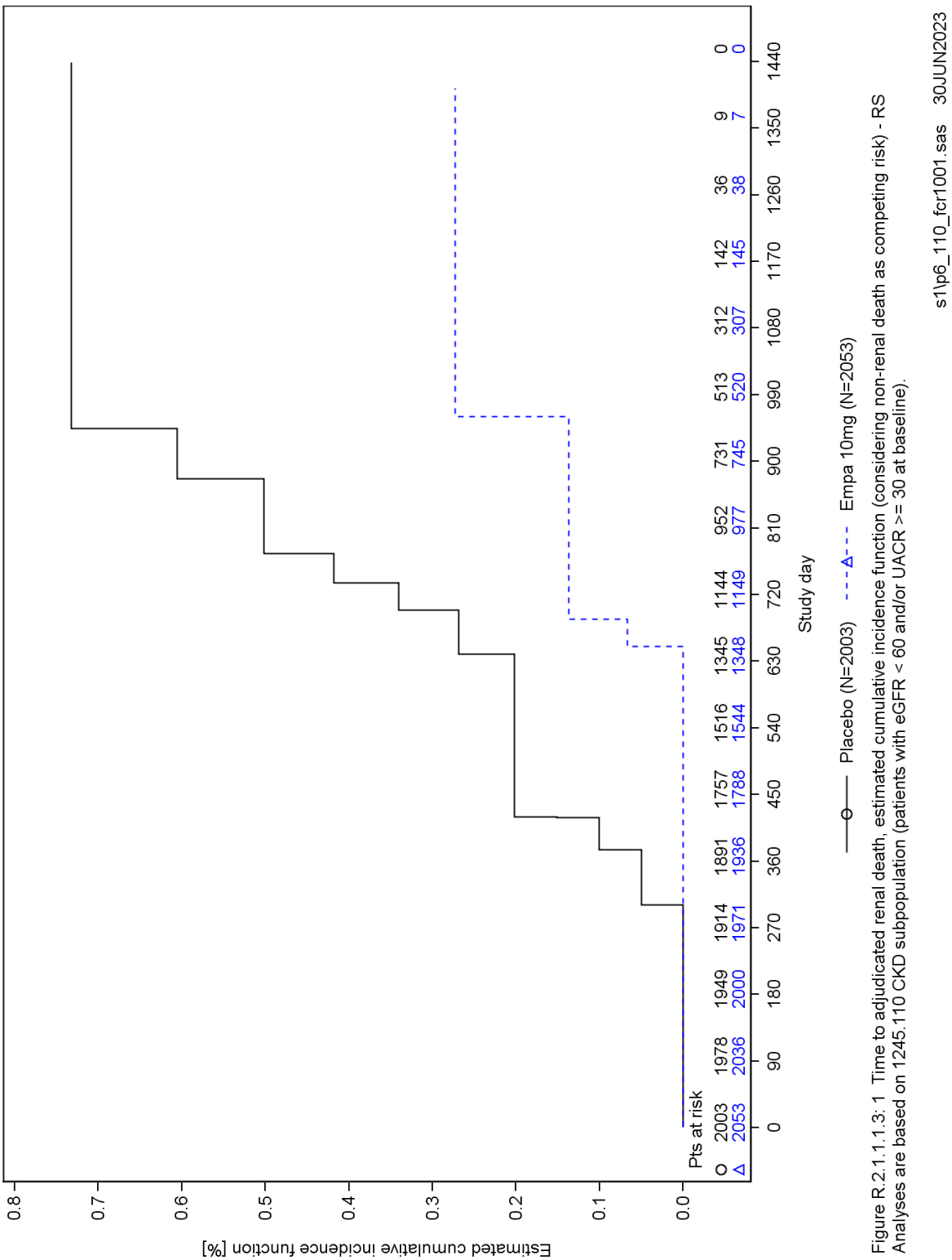


Figure R.2.1.1.1.3: 1 Time to adjudicated renal death, estimated cumulative incidence function (considering non-renal death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.2.1.1.2**

R.2.1.1.2.1 Time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death

Table R.2.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 277 | 13.8 | 8.29 | 2053 | 262 | 12.8 | 7.58 | 0.92 | (0.78,1.09) | 0.3469 | |
| Sex | | | | | | | | | | | | 0.4387 |
| Male | 1065 | 154 | 14.5 | 8.60 | 1094 | 155 | 14.2 | 8.37 | 0.98 | (0.78,1.22) | 0.8367 | |
| Female | 938 | 123 | 13.1 | 7.93 | 959 | 107 | 11.2 | 6.68 | 0.85 | (0.66,1.11) | 0.2303 | |
| Age [years] | | | | | | | | | | | | 0.2100 |
| <65 | 331 | 46 | 13.9 | 8.21 | 313 | 49 | 15.7 | 9.43 | 1.17 | (0.78,1.74) | 0.4558 | |
| >=65 | 1672 | 231 | 13.8 | 8.30 | 1740 | 213 | 12.2 | 7.26 | 0.88 | (0.73,1.06) | 0.1695 | |
| Region | | | | | | | | | | | | 0.6266 |
| North America | 273 | 34 | 12.5 | 7.52 | 274 | 36 | 13.1 | 7.81 | 1.00 | (0.63,1.60) | 0.9878 | |
| Latin America | 511 | 89 | 17.4 | 11.53 | 504 | 85 | 16.9 | 10.82 | 0.95 | (0.70,1.28) | 0.7235 | |
| Europe | 867 | 104 | 12.0 | 6.88 | 894 | 86 | 9.6 | 5.51 | 0.80 | (0.60,1.07) | 0.1333 | |
| Asia | 231 | 28 | 12.1 | 6.78 | 248 | 27 | 10.9 | 6.06 | 0.89 | (0.52,1.50) | 0.6547 | |
| Other | 121 | 22 | 18.2 | 11.28 | 133 | 28 | 21.1 | 13.91 | 1.31 | (0.75,2.29) | 0.3411 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3553 |
| Diabetic | 1046 | 158 | 15.1 | 9.22 | 1082 | 163 | 15.1 | 9.04 | 0.98 | (0.79,1.23) | 0.8897 | |
| Non-Diabetic | 957 | 119 | 12.4 | 7.30 | 971 | 99 | 10.2 | 6.00 | 0.84 | (0.64,1.09) | 0.1902 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1195 |
| <30 | 1087 | 166 | 15.3 | 9.36 | 1094 | 138 | 12.6 | 7.56 | 0.82 | (0.65,1.03) | 0.0847 | |
| >=30 | 916 | 111 | 12.1 | 7.07 | 959 | 124 | 12.9 | 7.61 | 1.08 | (0.83,1.39) | 0.5785 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.9655 |
| <130 | 827 | 100 | 12.1 | 7.30 | 853 | 94 | 11.0 | 6.59 | 0.93 | (0.70,1.23) | 0.5955 | |
| >=130 | 1176 | 177 | 15.1 | 8.97 | 1200 | 168 | 14.0 | 8.28 | 0.92 | (0.74,1.14) | 0.4344 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6817 |
| <75 | 936 | 132 | 14.1 | 8.51 | 935 | 119 | 12.7 | 7.59 | 0.89 | (0.69,1.14) | 0.3418 | |
| 75 to <85 | 658 | 93 | 14.1 | 8.27 | 703 | 86 | 12.2 | 7.26 | 0.89 | (0.66,1.19) | 0.4342 | |
| >=85 | 409 | 52 | 12.7 | 7.80 | 415 | 57 | 13.7 | 8.12 | 1.07 | (0.74,1.56) | 0.7185 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

Table R.2.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.0838 |
| <30 | 161 | 42 | 26.1 | 18.07 | 148 | 30 | 20.3 | 13.16 | 0.73 | (0.45,1.17) | 0.1855 | |
| 30 to <45 | 550 | 62 | 11.3 | 6.74 | 564 | 77 | 13.7 | 8.27 | 1.27 | (0.91,1.77) | 0.1652 | |
| >=45 | 1291 | 173 | 13.4 | 7.90 | 1341 | 155 | 11.6 | 6.75 | 0.85 | (0.68,1.06) | 0.1434 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9011 |
| Normal (<30) | 766 | 71 | 9.3 | 5.48 | 787 | 70 | 8.9 | 5.12 | 0.93 | (0.67,1.29) | 0.6686 | |
| Microalbuminuria (30 to <=300) | 921 | 130 | 14.1 | 8.38 | 939 | 116 | 12.4 | 7.39 | 0.90 | (0.70,1.16) | 0.4202 | |
| Macroalbuminuria (>300) | 311 | 76 | 24.4 | 15.50 | 318 | 76 | 23.9 | 15.04 | 0.99 | (0.72,1.37) | 0.9582 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4030 |
| Low, moderate or high | 1479 | 175 | 11.8 | 6.95 | 1549 | 164 | 10.6 | 6.16 | 0.89 | (0.72,1.10) | 0.2712 | |
| Very high | 519 | 102 | 19.7 | 12.45 | 495 | 98 | 19.8 | 12.56 | 1.03 | (0.78,1.36) | 0.8321 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9077 |
| No | 412 | 53 | 12.9 | 8.02 | 411 | 52 | 12.7 | 7.43 | 0.90 | (0.62,1.33) | 0.6047 | |
| Yes | 1591 | 224 | 14.1 | 8.35 | 1642 | 210 | 12.8 | 7.62 | 0.93 | (0.77,1.12) | 0.4300 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.2726 |
| No | 282 | 41 | 14.5 | 8.98 | 277 | 42 | 15.2 | 9.74 | 1.16 | (0.75,1.78) | 0.5087 | |
| Yes | 1721 | 236 | 13.7 | 8.18 | 1776 | 220 | 12.4 | 7.28 | 0.89 | (0.74,1.07) | 0.2117 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3350 |
| No | 229 | 31 | 13.5 | 7.72 | 250 | 22 | 8.8 | 5.24 | 0.71 | (0.41,1.23) | 0.2266 | |
| Yes | 1774 | 246 | 13.9 | 8.36 | 1803 | 240 | 13.3 | 7.91 | 0.95 | (0.79,1.13) | 0.5493 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

**Figure R.2.1.1.2.1: 1**

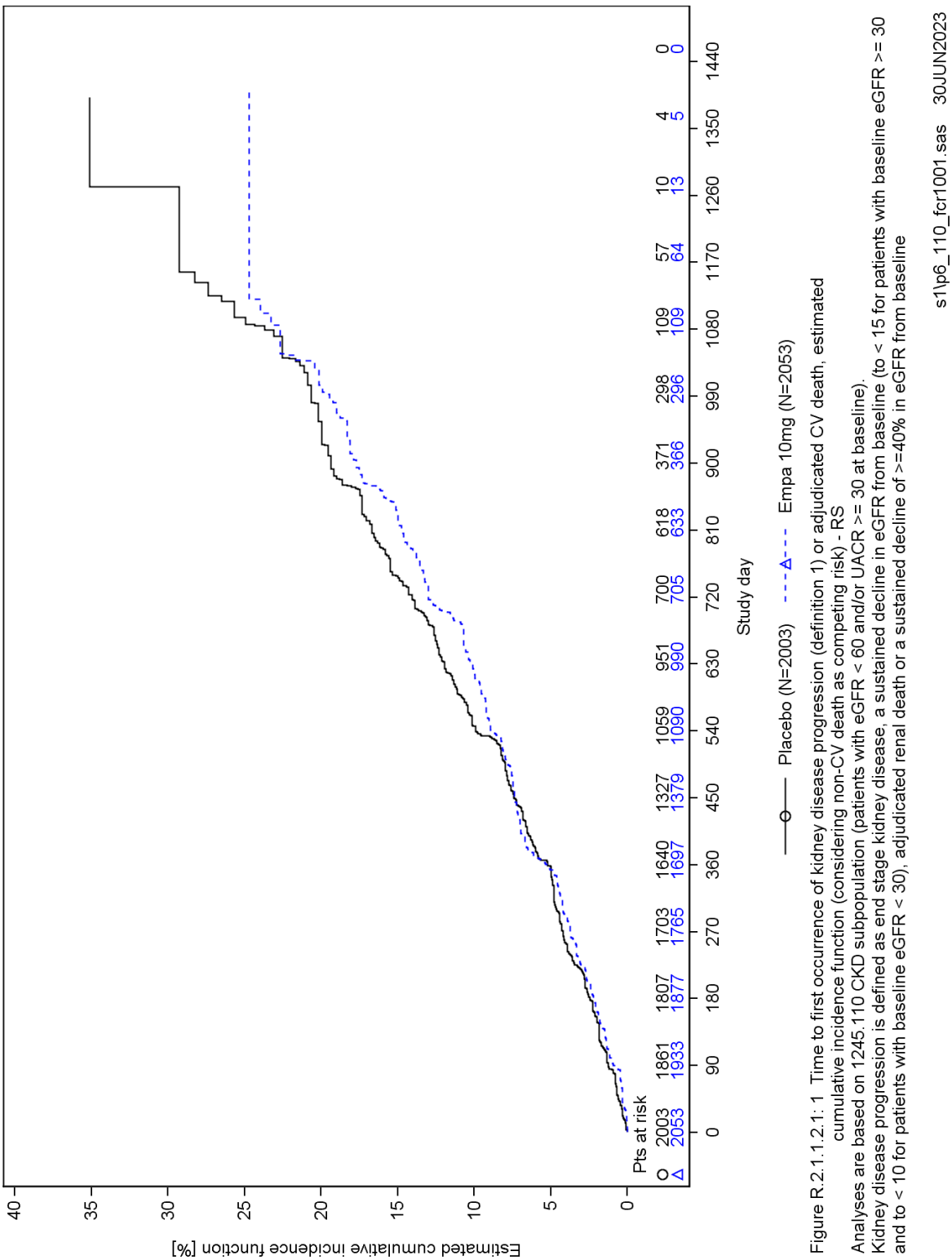


Figure R.2.1.1.2.1: 1 Time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

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R.2.1.1.2.2 Time to first occurrence of kidney disease progression (definition 1)

Table R.2.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 93 | 4.6 | 2.84 | 2053 | 93 | 4.5 | 2.75 | 0.97 | (0.73,1.30) | 0.8446 | |
| Sex | | | | | | | | | | | | 0.5365 |
| Male | 1065 | 46 | 4.3 | 2.63 | 1094 | 51 | 4.7 | 2.81 | 1.06 | (0.71,1.58) | 0.7746 | |
| Female | 938 | 47 | 5.0 | 3.08 | 959 | 42 | 4.4 | 2.67 | 0.88 | (0.58,1.34) | 0.5608 | |
| Age [years] | | | | | | | | | | | | 0.4752 |
| <65 | 331 | 23 | 6.9 | 4.16 | 313 | 25 | 8.0 | 4.87 | 1.18 | (0.67,2.07) | 0.5760 | |
| >=65 | 1672 | 70 | 4.2 | 2.57 | 1740 | 68 | 3.9 | 2.37 | 0.92 | (0.66,1.29) | 0.6472 | |
| Region | | | | | | | | | | | | 0.9060 |
| North America | 273 | 14 | 5.1 | 3.15 | 274 | 11 | 4.0 | 2.45 | 0.77 | (0.35,1.69) | 0.5071 | |
| Latin America | 511 | 31 | 6.1 | 4.10 | 504 | 28 | 5.6 | 3.66 | 0.87 | (0.52,1.46) | 0.6067 | |
| Europe | 867 | 22 | 2.5 | 1.49 | 894 | 23 | 2.6 | 1.50 | 1.00 | (0.56,1.80) | 0.9890 | |
| Asia | 231 | 13 | 5.6 | 3.17 | 248 | 17 | 6.9 | 3.84 | 1.17 | (0.57,2.41) | 0.6713 | |
| Other | 121 | 13 | 10.7 | 6.75 | 133 | 14 | 10.5 | 7.17 | 1.18 | (0.55,2.50) | 0.6736 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3221 |
| Diabetic | 1046 | 62 | 5.9 | 3.70 | 1082 | 69 | 6.4 | 3.91 | 1.07 | (0.76,1.51) | 0.7004 | |
| Non-Diabetic | 957 | 31 | 3.2 | 1.94 | 971 | 24 | 2.5 | 1.48 | 0.78 | (0.46,1.32) | 0.3524 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.4302 |
| <30 | 1087 | 50 | 4.6 | 2.88 | 1094 | 43 | 3.9 | 2.40 | 0.86 | (0.58,1.30) | 0.4856 | |
| >=30 | 916 | 43 | 4.7 | 2.79 | 959 | 50 | 5.2 | 3.13 | 1.09 | (0.73,1.64) | 0.6758 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7712 |
| <130 | 827 | 30 | 3.6 | 2.23 | 853 | 26 | 3.0 | 1.86 | 0.90 | (0.53,1.52) | 0.6905 | |
| >=130 | 1176 | 63 | 5.4 | 3.26 | 1200 | 67 | 5.6 | 3.37 | 0.99 | (0.70,1.39) | 0.9392 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3827 |
| <75 | 936 | 44 | 4.7 | 2.89 | 935 | 34 | 3.6 | 2.21 | 0.76 | (0.49,1.20) | 0.2379 | |
| 75 to <85 | 658 | 27 | 4.1 | 2.46 | 703 | 33 | 4.7 | 2.84 | 1.14 | (0.69,1.90) | 0.6067 | |
| >=85 | 409 | 22 | 5.4 | 3.35 | 415 | 26 | 6.3 | 3.78 | 1.17 | (0.66,2.07) | 0.5844 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

Table R.2.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2308 |
| <30 | 161 | 20 | 12.4 | 8.90 | 148 | 13 | 8.8 | 5.88 | 0.56 | (0.28,1.13) | 0.1030 | |
| 30 to <45 | 550 | 24 | 4.4 | 2.65 | 564 | 28 | 5.0 | 3.06 | 1.16 | (0.67,2.01) | 0.5843 | |
| >=45 | 1291 | 49 | 3.8 | 2.28 | 1341 | 52 | 3.9 | 2.31 | 1.04 | (0.70,1.53) | 0.8535 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7187 |
| Normal (<30) | 766 | 17 | 2.2 | 1.33 | 787 | 21 | 2.7 | 1.56 | 1.21 | (0.64,2.29) | 0.5607 | |
| Microalbuminuria (30 to <=300) | 921 | 38 | 4.1 | 2.50 | 939 | 34 | 3.6 | 2.22 | 0.92 | (0.58,1.46) | 0.7122 | |
| Macroalbuminuria (>300) | 311 | 38 | 12.2 | 7.99 | 318 | 38 | 11.9 | 7.73 | 0.89 | (0.56,1.39) | 0.5976 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3476 |
| Low, moderate or high | 1479 | 48 | 3.2 | 1.94 | 1549 | 55 | 3.6 | 2.10 | 1.11 | (0.75,1.64) | 0.5910 | |
| Very high | 519 | 45 | 8.7 | 5.63 | 495 | 38 | 7.7 | 5.00 | 0.84 | (0.55,1.30) | 0.4349 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9007 |
| No | 412 | 16 | 3.9 | 2.47 | 411 | 17 | 4.1 | 2.49 | 0.94 | (0.47,1.86) | 0.8555 | |
| Yes | 1591 | 77 | 4.8 | 2.93 | 1642 | 76 | 4.6 | 2.81 | 0.98 | (0.72,1.35) | 0.9237 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3968 |
| No | 282 | 14 | 5.0 | 3.12 | 277 | 16 | 5.8 | 3.80 | 1.30 | (0.63,2.67) | 0.4738 | |
| Yes | 1721 | 79 | 4.6 | 2.79 | 1776 | 77 | 4.3 | 2.60 | 0.93 | (0.68,1.27) | 0.6326 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.5981 |
| No | 229 | 7 | 3.1 | 1.78 | 250 | 5 | 2.0 | 1.21 | 0.72 | (0.23,2.27) | 0.5729 | |
| Yes | 1774 | 86 | 4.8 | 2.98 | 1803 | 88 | 4.9 | 2.96 | 0.99 | (0.73,1.33) | 0.9415 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

**Figure R.2.1.1.2.2: 1**

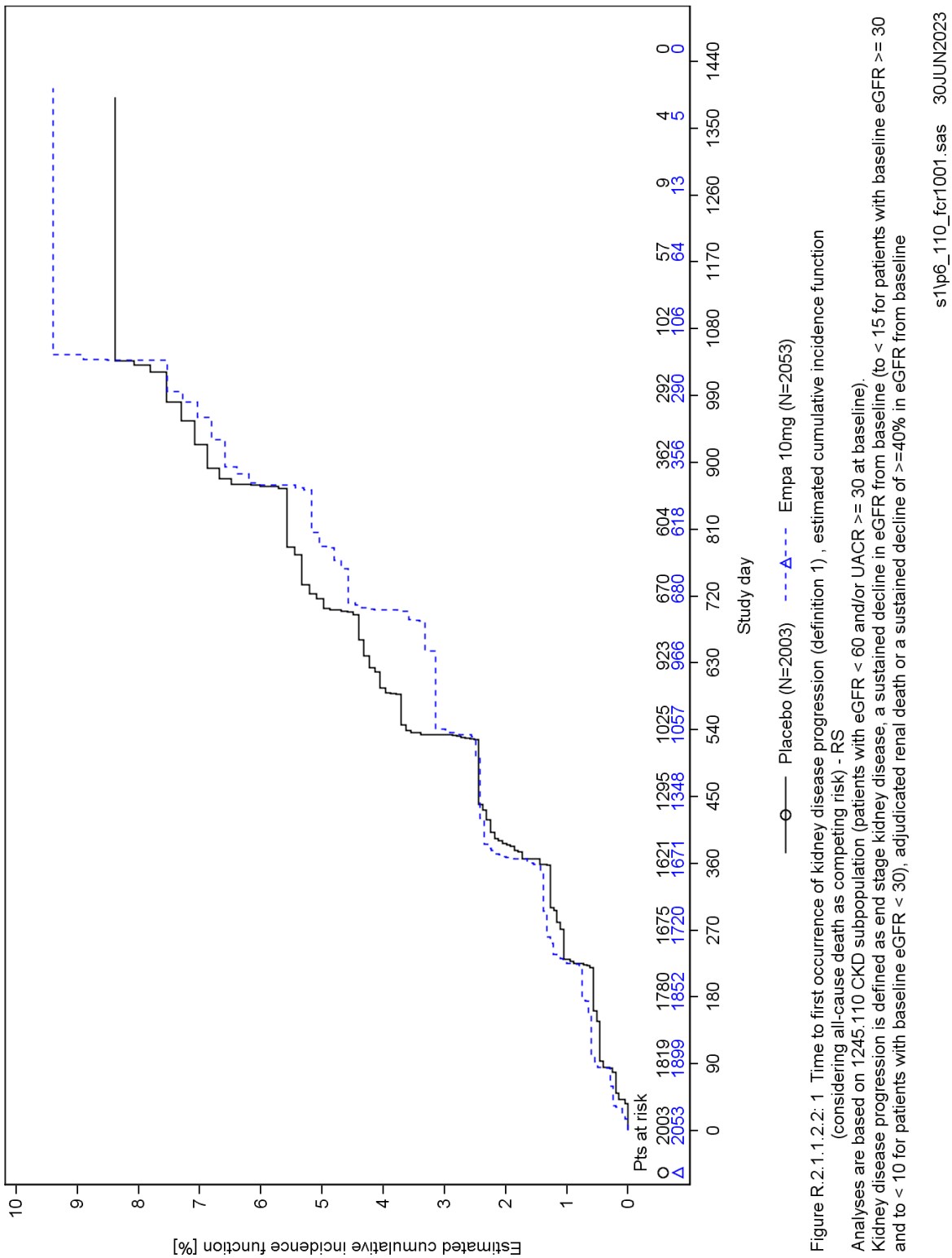


Figure R.2.1.1.2.2: 1 Time to first occurrence of kidney disease progression (definition 1) , estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

R.2.1.1.2.3 Time to first occurrence of kidney disease progression (definition 2)

Table R.2.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 56 | 2.8 | 1.69 | 2053 | 43 | 2.1 | 1.26 | 0.73 | (0.49,1.09) | 0.1259 | |
| Sex | | | | | | | | | | | | 0.5621 |
| Male | 1065 | 32 | 3.0 | 1.82 | 1094 | 28 | 2.6 | 1.53 | 0.80 | (0.48,1.34) | 0.4031 | |
| Female | 938 | 24 | 2.6 | 1.55 | 959 | 15 | 1.6 | 0.94 | 0.63 | (0.33,1.20) | 0.1625 | |
| Age [years] | | | | | | | | | | | | 0.6288 |
| <65 | 331 | 17 | 5.1 | 3.05 | 313 | 14 | 4.5 | 2.68 | 0.87 | (0.43,1.76) | 0.6902 | |
| >=65 | 1672 | 39 | 2.3 | 1.42 | 1740 | 29 | 1.7 | 1.00 | 0.70 | (0.43,1.13) | 0.1473 | |
| Region | | | | | | | | | | | | 0.9942 |
| North America | 273 | 12 | 4.4 | 2.68 | 274 | 8 | 2.9 | 1.77 | 0.63 | (0.26,1.54) | 0.3124 | |
| Latin America | 511 | 18 | 3.5 | 2.34 | 504 | 14 | 2.8 | 1.81 | 0.75 | (0.37,1.52) | 0.4267 | |
| Europe | 867 | 11 | 1.3 | 0.74 | 894 | 9 | 1.0 | 0.58 | 0.77 | (0.32,1.85) | 0.5569 | |
| Asia | 231 | 7 | 3.0 | 1.69 | 248 | 7 | 2.8 | 1.56 | 0.85 | (0.30,2.43) | 0.7635 | |
| Other | 121 | 8 | 6.6 | 4.10 | 133 | 5 | 3.8 | 2.48 | 0.68 | (0.22,2.07) | 0.4957 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2606 |
| Diabetic | 1046 | 41 | 3.9 | 2.42 | 1082 | 36 | 3.3 | 2.01 | 0.83 | (0.53,1.30) | 0.4167 | |
| Non-Diabetic | 957 | 15 | 1.6 | 0.93 | 971 | 7 | 0.7 | 0.43 | 0.47 | (0.19,1.14) | 0.0960 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.6411 |
| <30 | 1087 | 29 | 2.7 | 1.65 | 1094 | 19 | 1.7 | 1.05 | 0.66 | (0.37,1.19) | 0.1669 | |
| >=30 | 916 | 27 | 2.9 | 1.74 | 959 | 24 | 2.5 | 1.48 | 0.80 | (0.46,1.40) | 0.4379 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5380 |
| <130 | 827 | 16 | 1.9 | 1.18 | 853 | 9 | 1.1 | 0.64 | 0.57 | (0.25,1.31) | 0.1858 | |
| >=130 | 1176 | 40 | 3.4 | 2.05 | 1200 | 34 | 2.8 | 1.69 | 0.77 | (0.49,1.22) | 0.2723 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6998 |
| <75 | 936 | 22 | 2.4 | 1.43 | 935 | 20 | 2.1 | 1.29 | 0.88 | (0.48,1.62) | 0.6823 | |
| 75 to <85 | 658 | 16 | 2.4 | 1.44 | 703 | 10 | 1.4 | 0.85 | 0.58 | (0.26,1.28) | 0.1759 | |
| >=85 | 409 | 18 | 4.4 | 2.71 | 415 | 13 | 3.1 | 1.87 | 0.69 | (0.34,1.43) | 0.3202 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 50% in eGFR from baseline.

Table R.2.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4822 |
| <30 | 161 | 13 | 8.1 | 5.72 | 148 | 9 | 6.1 | 4.04 | 0.53 | (0.23,1.26) | 0.1500 | |
| 30 to <45 | 550 | 12 | 2.2 | 1.31 | 564 | 13 | 2.3 | 1.40 | 1.06 | (0.48,2.33) | 0.8838 | |
| >=45 | 1291 | 31 | 2.4 | 1.43 | 1341 | 21 | 1.6 | 0.92 | 0.68 | (0.39,1.18) | 0.1670 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9259 |
| Normal (<30) | 766 | 7 | 0.9 | 0.54 | 787 | 4 | 0.5 | 0.29 | 0.57 | (0.17,1.94) | 0.3660 | |
| Microalbuminuria (30 to <=300) | 921 | 22 | 2.4 | 1.44 | 939 | 16 | 1.7 | 1.04 | 0.73 | (0.38,1.40) | 0.3474 | |
| Macroalbuminuria (>300) | 311 | 27 | 8.7 | 5.58 | 318 | 23 | 7.2 | 4.58 | 0.74 | (0.42,1.29) | 0.2880 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.8387 |
| Low, moderate or high | 1479 | 27 | 1.8 | 1.08 | 1549 | 19 | 1.2 | 0.72 | 0.70 | (0.39,1.27) | 0.2412 | |
| Very high | 519 | 29 | 5.6 | 3.58 | 495 | 24 | 4.8 | 3.12 | 0.76 | (0.44,1.32) | 0.3340 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9844 |
| No | 412 | 12 | 2.9 | 1.85 | 411 | 10 | 2.4 | 1.46 | 0.74 | (0.32,1.71) | 0.4769 | |
| Yes | 1591 | 44 | 2.8 | 1.65 | 1642 | 33 | 2.0 | 1.21 | 0.73 | (0.46,1.15) | 0.1736 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4862 |
| No | 282 | 10 | 3.5 | 2.22 | 277 | 9 | 3.2 | 2.11 | 0.99 | (0.40,2.45) | 0.9833 | |
| Yes | 1721 | 46 | 2.7 | 1.61 | 1776 | 34 | 1.9 | 1.14 | 0.69 | (0.44,1.08) | 0.1052 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.1571 |
| No | 229 | 6 | 2.6 | 1.51 | 250 | 1 | 0.4 | 0.24 | 0.17 | (0.02,1.39) | 0.0982 | |
| Yes | 1774 | 50 | 2.8 | 1.72 | 1803 | 42 | 2.3 | 1.40 | 0.80 | (0.53,1.20) | 0.2760 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 50% in eGFR from baseline.

**Figure R.2.1.1.2.3: 1**

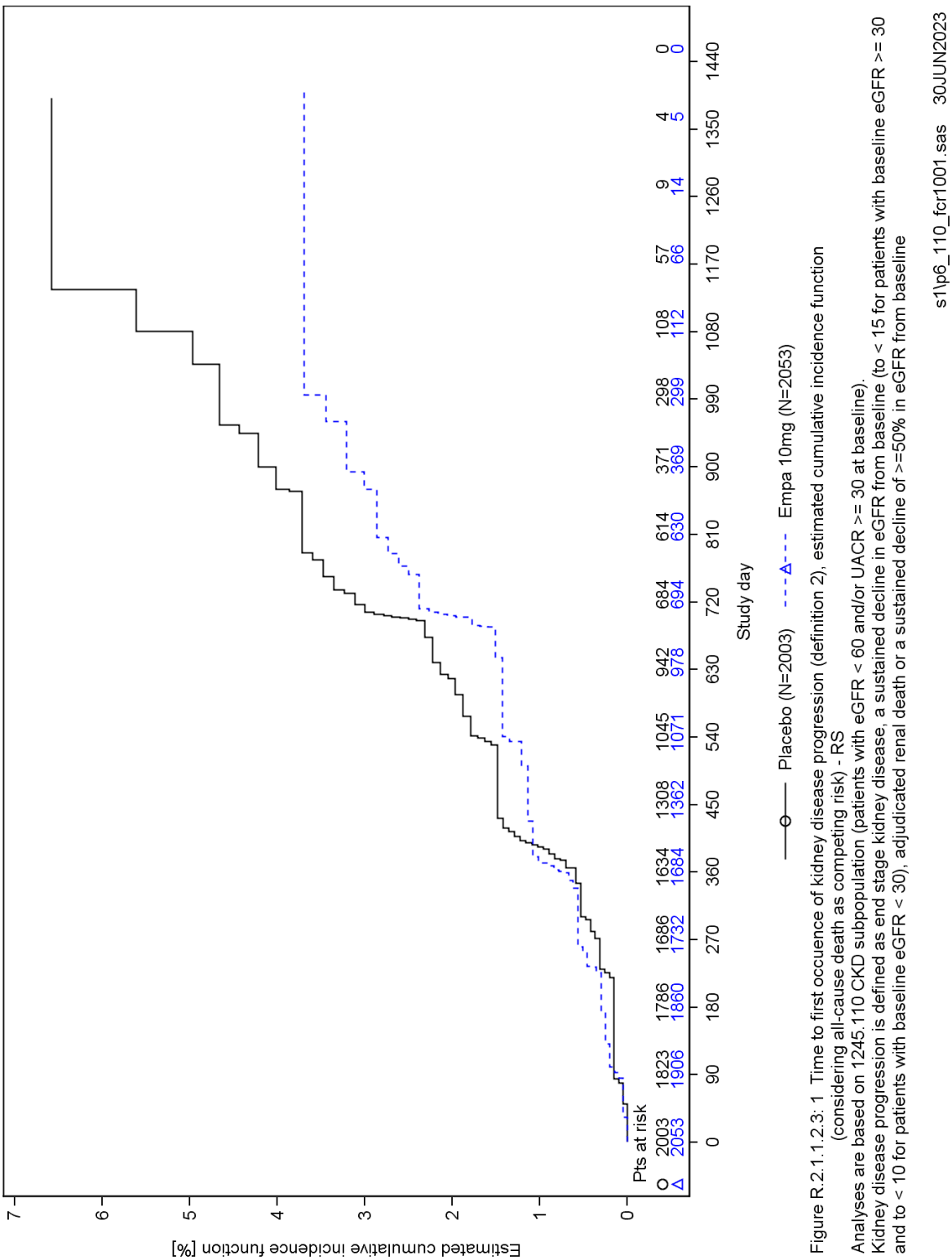


Figure R.2.1.1.2.3: 1 Time to first occuence of kidney disease progression (definition 2), estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=50% in eGFR from baseline

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R.2.1.1.2.4 Time to first occurrence of kidney disease progression (definition 3)

Table R.2.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 36 | 1.8 | 1.08 | 2053 | 33 | 1.6 | 0.96 | 0.86 | (0.54,1.39) | 0.5397 | |
| Sex | | | | | | | | | | | | 0.8143 |
| Male | 1065 | 21 | 2.0 | 1.19 | 1094 | 21 | 1.9 | 1.14 | 0.90 | (0.49,1.66) | 0.7398 | |
| Female | 938 | 15 | 1.6 | 0.97 | 959 | 12 | 1.3 | 0.75 | 0.80 | (0.38,1.72) | 0.5715 | |
| Age [years] | | | | | | | | | | | | 0.8844 |
| <65 | 331 | 11 | 3.3 | 1.96 | 313 | 10 | 3.2 | 1.91 | 0.93 | (0.39,2.20) | 0.8686 | |
| >=65 | 1672 | 25 | 1.5 | 0.91 | 1740 | 23 | 1.3 | 0.79 | 0.86 | (0.49,1.52) | 0.6071 | |
| Region | | | | | | | | | | | | 0.9853 |
| North America | 273 | 8 | 2.9 | 1.78 | 274 | 7 | 2.6 | 1.55 | 0.83 | (0.30,2.28) | 0.7117 | |
| Latin America | 511 | 13 | 2.5 | 1.68 | 504 | 12 | 2.4 | 1.55 | 0.88 | (0.40,1.94) | 0.7529 | |
| Europe | 867 | 5 | 0.6 | 0.34 | 894 | 6 | 0.7 | 0.39 | 1.12 | (0.34,3.67) | 0.8538 | |
| Asia | 231 | 5 | 2.2 | 1.20 | 248 | 5 | 2.0 | 1.10 | 0.82 | (0.24,2.85) | 0.7572 | |
| Other | 121 | 5 | 4.1 | 2.54 | 133 | 3 | 2.3 | 1.48 | 0.64 | (0.15,2.69) | 0.5429 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2270 |
| Diabetic | 1046 | 27 | 2.6 | 1.59 | 1082 | 29 | 2.7 | 1.62 | 1.00 | (0.59,1.69) | 0.9996 | |
| Non-Diabetic | 957 | 9 | 0.9 | 0.56 | 971 | 4 | 0.4 | 0.24 | 0.45 | (0.14,1.47) | 0.1856 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5712 |
| <30 | 1087 | 20 | 1.8 | 1.14 | 1094 | 15 | 1.4 | 0.83 | 0.76 | (0.39,1.48) | 0.4156 | |
| >=30 | 916 | 16 | 1.7 | 1.03 | 959 | 18 | 1.9 | 1.11 | 1.00 | (0.51,1.96) | 0.9916 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0498 |
| <130 | 827 | 14 | 1.7 | 1.03 | 853 | 5 | 0.6 | 0.35 | 0.36 | (0.13,0.99) | 0.0482 | |
| >=130 | 1176 | 22 | 1.9 | 1.12 | 1200 | 28 | 2.3 | 1.39 | 1.15 | (0.65,2.02) | 0.6263 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.1120 |
| <75 | 936 | 13 | 1.4 | 0.85 | 935 | 16 | 1.7 | 1.03 | 1.18 | (0.57,2.46) | 0.6590 | |
| 75 to <85 | 658 | 15 | 2.3 | 1.35 | 703 | 6 | 0.9 | 0.51 | 0.37 | (0.14,0.96) | 0.0413 | |
| >=85 | 409 | 8 | 2.0 | 1.19 | 415 | 11 | 2.7 | 1.58 | 1.28 | (0.51,3.21) | 0.6012 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 57% in eGFR from baseline.

Table R.2.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6681 |
| <30 | 161 | 10 | 6.2 | 4.39 | 148 | 9 | 6.1 | 4.04 | 0.69 | (0.28,1.70) | 0.4161 | |
| 30 to <45 | 550 | 11 | 2.0 | 1.20 | 564 | 8 | 1.4 | 0.86 | 0.70 | (0.28,1.74) | 0.4409 | |
| >=45 | 1291 | 15 | 1.2 | 0.69 | 1341 | 16 | 1.2 | 0.70 | 1.07 | (0.53,2.17) | 0.8458 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9660 |
| Normal (<30) | 766 | 4 | 0.5 | 0.31 | 787 | 3 | 0.4 | 0.22 | 0.76 | (0.17,3.38) | 0.7135 | |
| Microalbuminuria (30 to <=300) | 921 | 13 | 1.4 | 0.85 | 939 | 12 | 1.3 | 0.77 | 0.91 | (0.41,2.00) | 0.8186 | |
| Macroalbuminuria (>300) | 311 | 19 | 6.1 | 3.91 | 318 | 18 | 5.7 | 3.57 | 0.81 | (0.42,1.56) | 0.5379 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2208 |
| Low, moderate or high | 1479 | 12 | 0.8 | 0.48 | 1549 | 15 | 1.0 | 0.57 | 1.26 | (0.59,2.69) | 0.5551 | |
| Very high | 519 | 24 | 4.6 | 2.96 | 495 | 18 | 3.6 | 2.33 | 0.68 | (0.37,1.26) | 0.2229 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5457 |
| No | 412 | 8 | 1.9 | 1.23 | 411 | 6 | 1.5 | 0.87 | 0.65 | (0.22,1.86) | 0.4179 | |
| Yes | 1591 | 28 | 1.8 | 1.05 | 1642 | 27 | 1.6 | 0.99 | 0.93 | (0.55,1.58) | 0.7884 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.2538 |
| No | 282 | 5 | 1.8 | 1.10 | 277 | 7 | 2.5 | 1.64 | 1.61 | (0.51,5.08) | 0.4201 | |
| Yes | 1721 | 31 | 1.8 | 1.08 | 1776 | 26 | 1.5 | 0.87 | 0.77 | (0.45,1.30) | 0.3244 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9800 |
| No | 229 | 2 | 0.9 | 0.50 | 250 | 0 | 0 | 0.00 | <0.01 | | 0.9799 | |
| Yes | 1774 | 34 | 1.9 | 1.16 | 1803 | 33 | 1.8 | 1.10 | 0.90 | (0.56,1.46) | 0.6826 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 57% in eGFR from baseline.

**Figure R.2.1.1.2.4: 1**

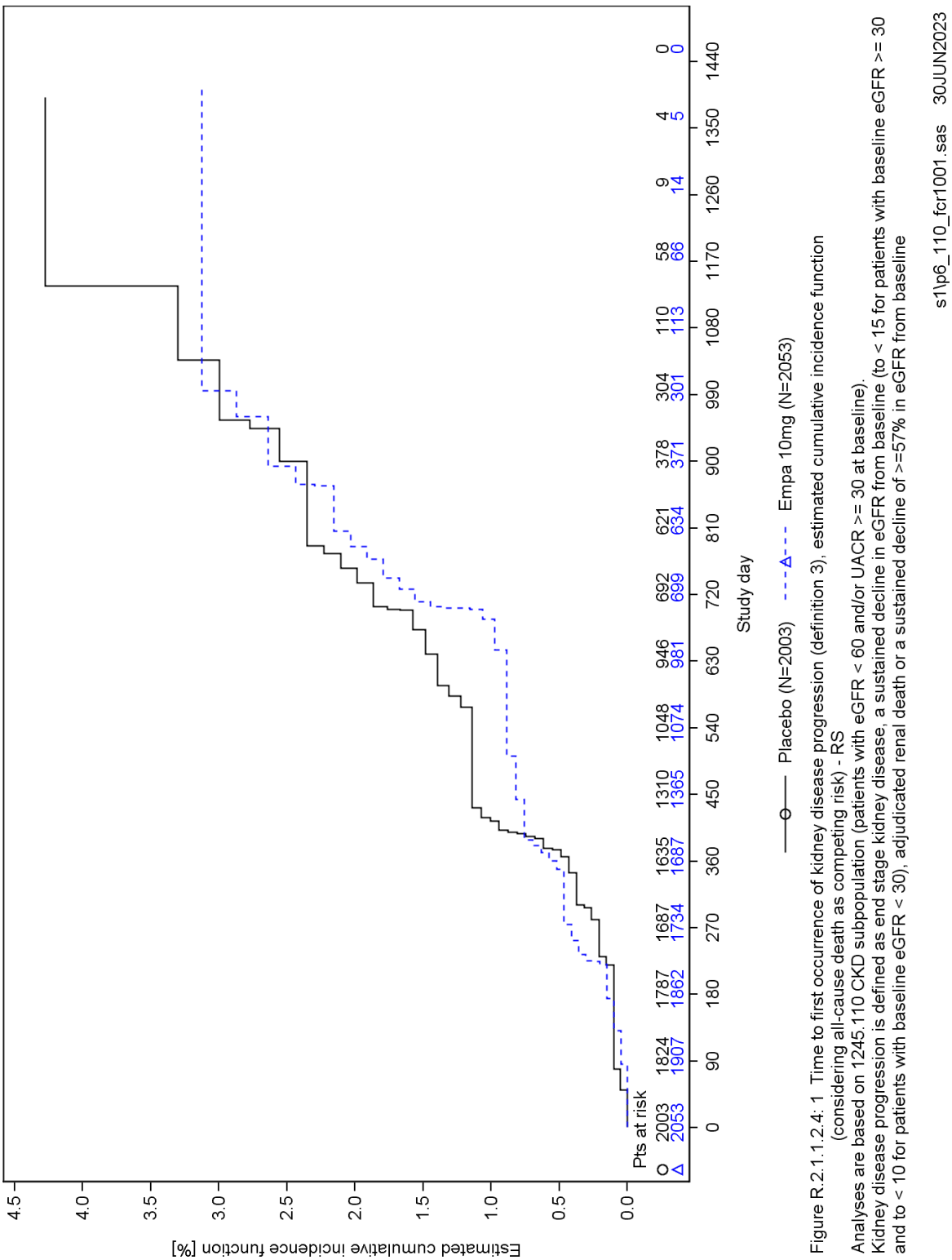


Figure R.2.1.1.2.4: 1 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=57% in eGFR from baseline

**Figure R.2.1.1.2.4: 2**

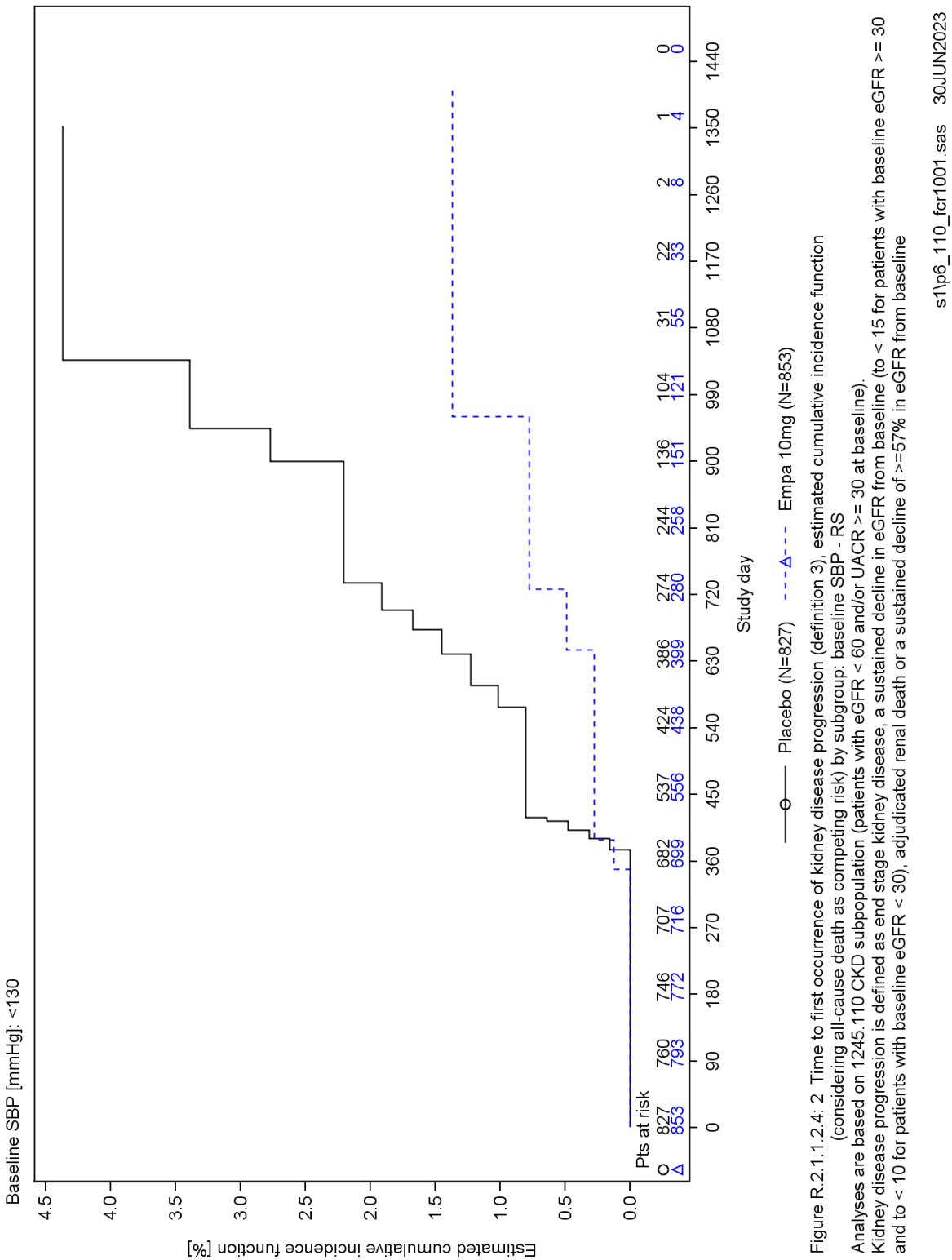


Figure R.2.1.1.2.4: 2 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=57% in eGFR from baseline

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**Figure R.2.1.1.2.4: 2**

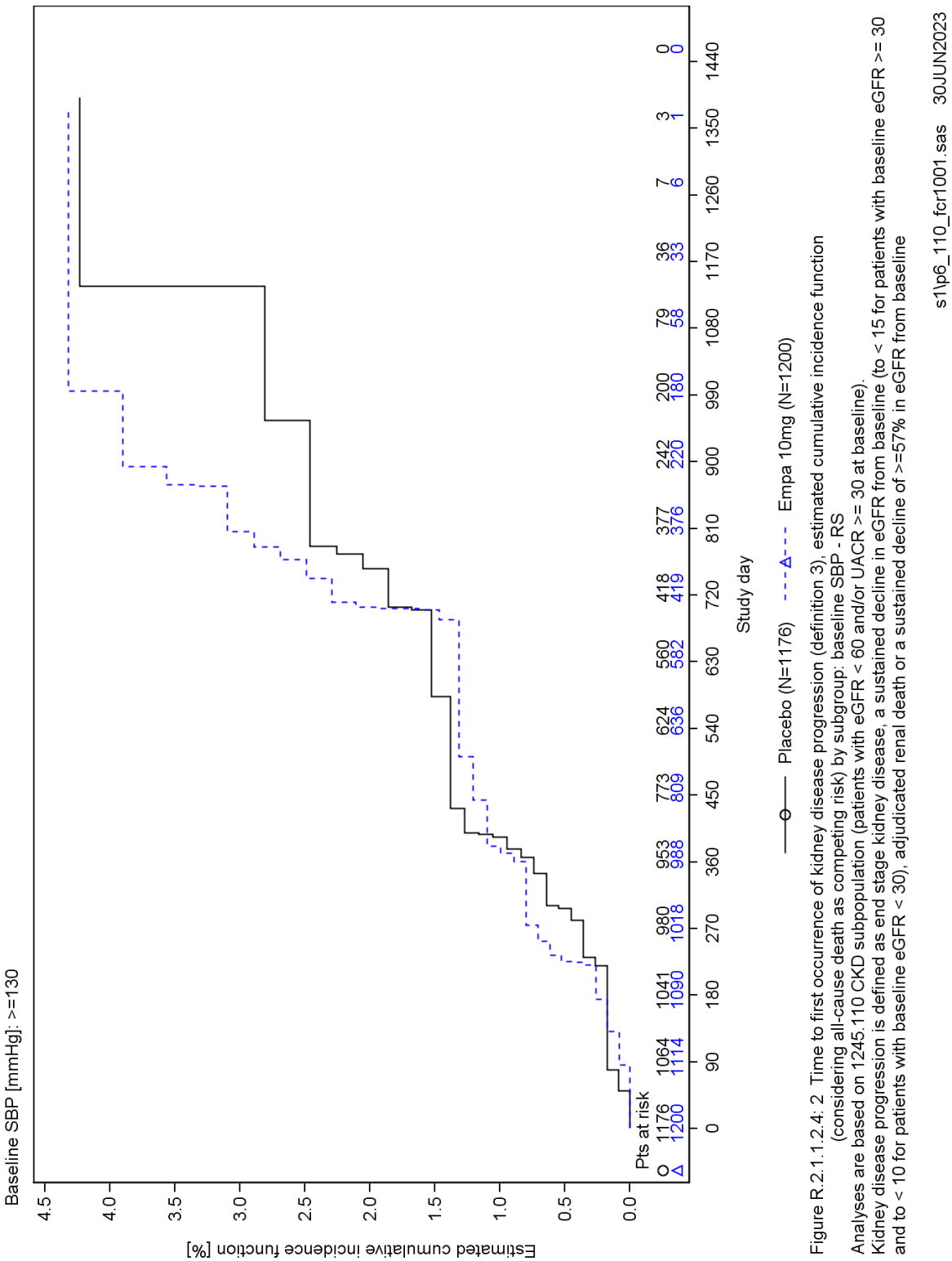


Figure R.2.1.1.2.4: 2 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=57% in eGFR from baseline

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R.2.1.1.2.5 Time to first occurrence of sustained decline of >= 40% in eGFR

Table R.2.1.1.2.5: 1 Cox Regression for time to first occurrence of sustained decline of >= 40% in eGFR until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2003 | 81 | 4.0 | 2.47 | 2053 | 83 | 4.0 | 2.45 | 1.00 | (0.73,1.35) | 0.9755 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.2.5: 1**

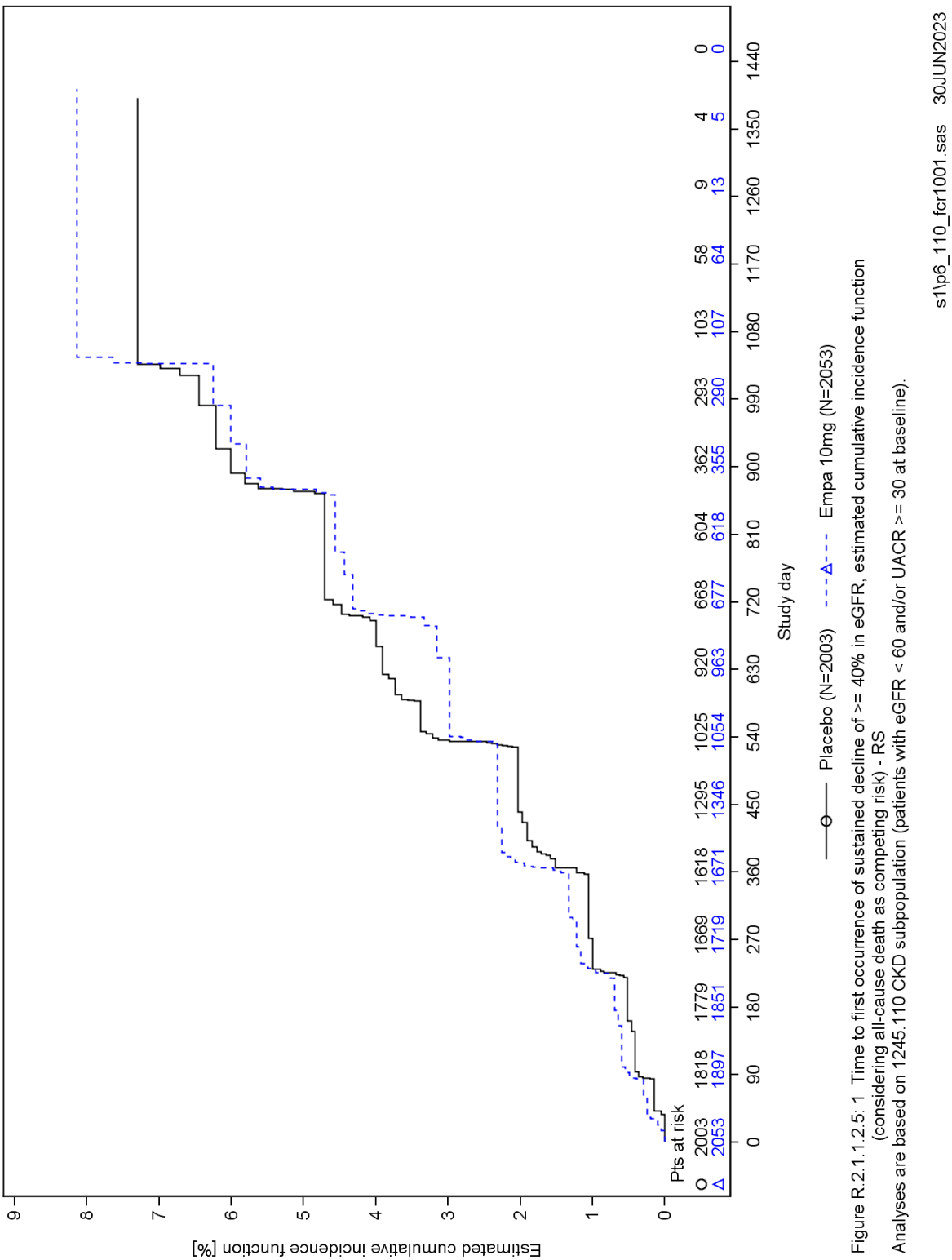


Figure R.2.1.1.2.5: 1 Time to first occurrence of sustained decline of >= 40% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.2.1.1.2.6 Time to first occurrence of sustained decline of >= 50% in eGFR

Table R.2.1.1.2.6: 1 Cox Regression for time to first occurrence of sustained decline of >= 50% in eGFR until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2003 | 42 | 2.1 | 1.27 | 2053 | 33 | 1.6 | 0.97 | 0.76 | (0.48,1.19) | 0.2291 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.2.6: 1**

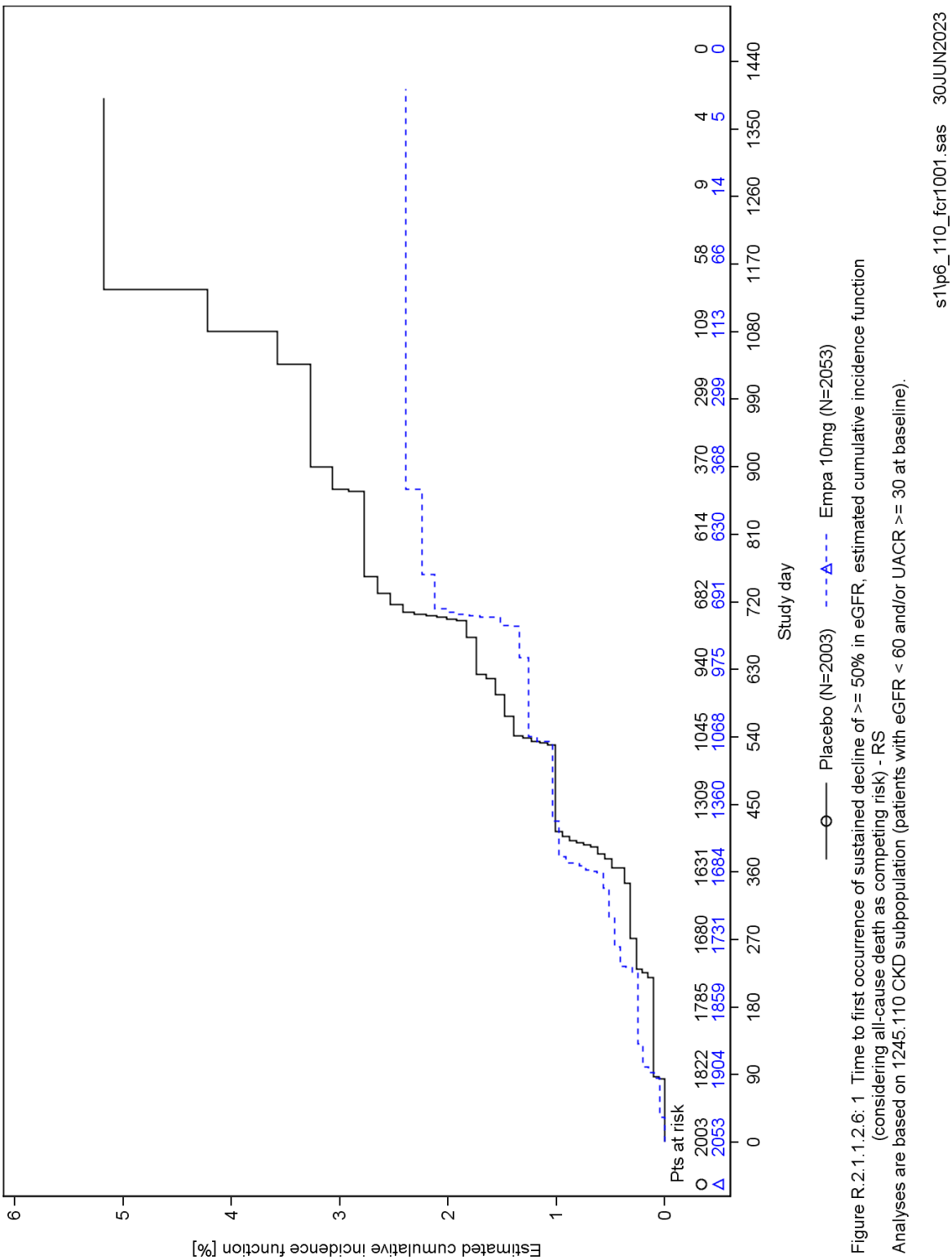


Figure R.2.1.1.2.6: 1 Time to first occurrence of sustained decline of >= 50% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.2.1.1.2.7 Time to first occurrence of sustained decline of >= 57% in eGFR

Table R.2.1.1.2.7: 1 Cox Regression for time to first occurrence of sustained decline of >= 57% in eGFR until the end of planned treatment period overall - RS

| Subgroup Category | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 22 | 1.1 | 0.66 | 2053 | 22 | 1.1 | 0.64 | 0.95 | (0.52,1.71) | 0.8536 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.2.7: 1**

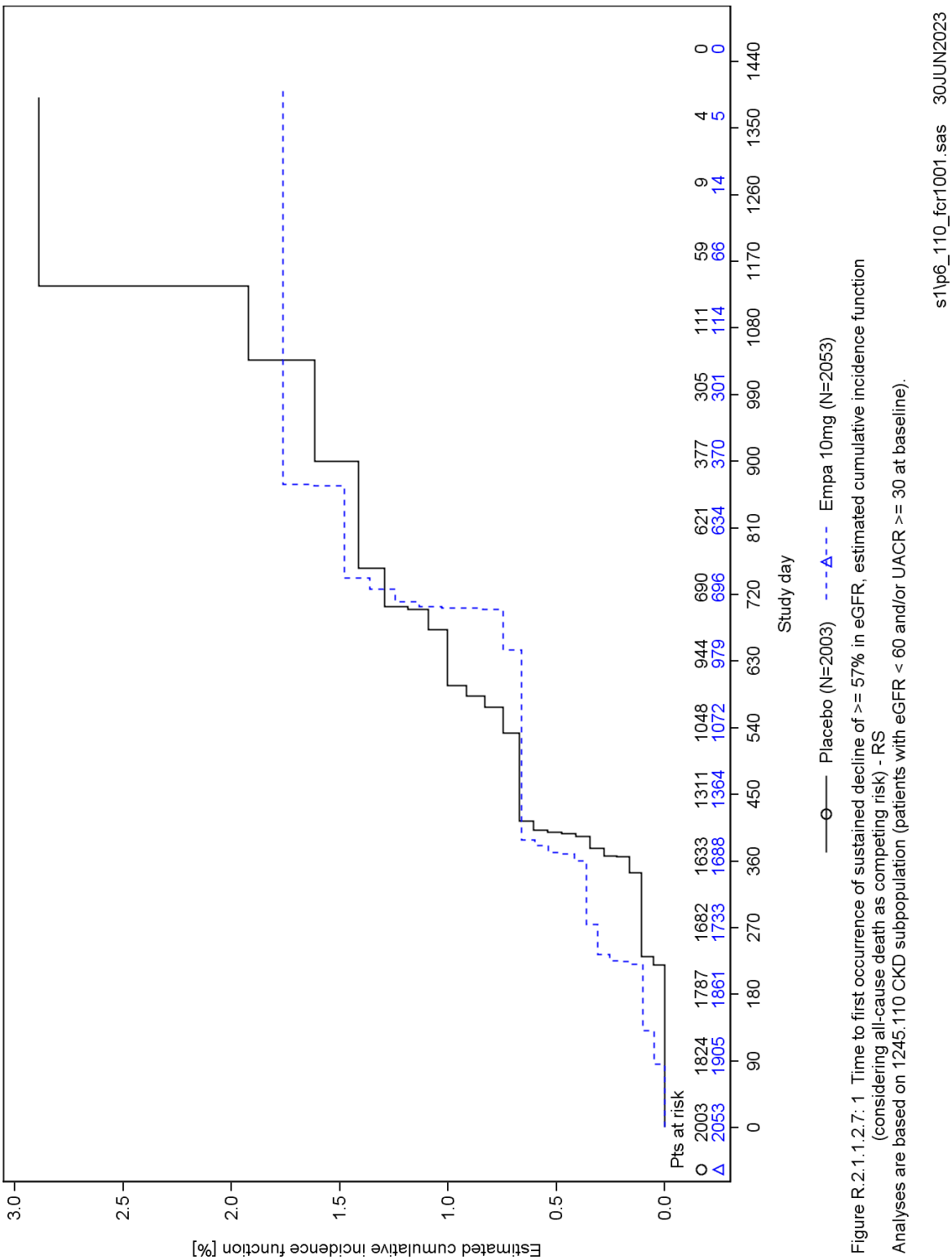


Figure R.2.1.1.2.7: 1 Time to first occurrence of sustained decline of >= 57% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.2.1.1.2.8**

R.2.1.1.2.8 Time to ESKD

Table R.2.1.1.2.8: 1 Cox Regression for time to ESKD until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2003 | 11 | 0.5 | 0.27 | 2053 | 10 | 0.5 | 0.24 | 0.82 | (0.35,1.94) | 0.6489 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

**Figure R.2.1.1.2.8: 1**

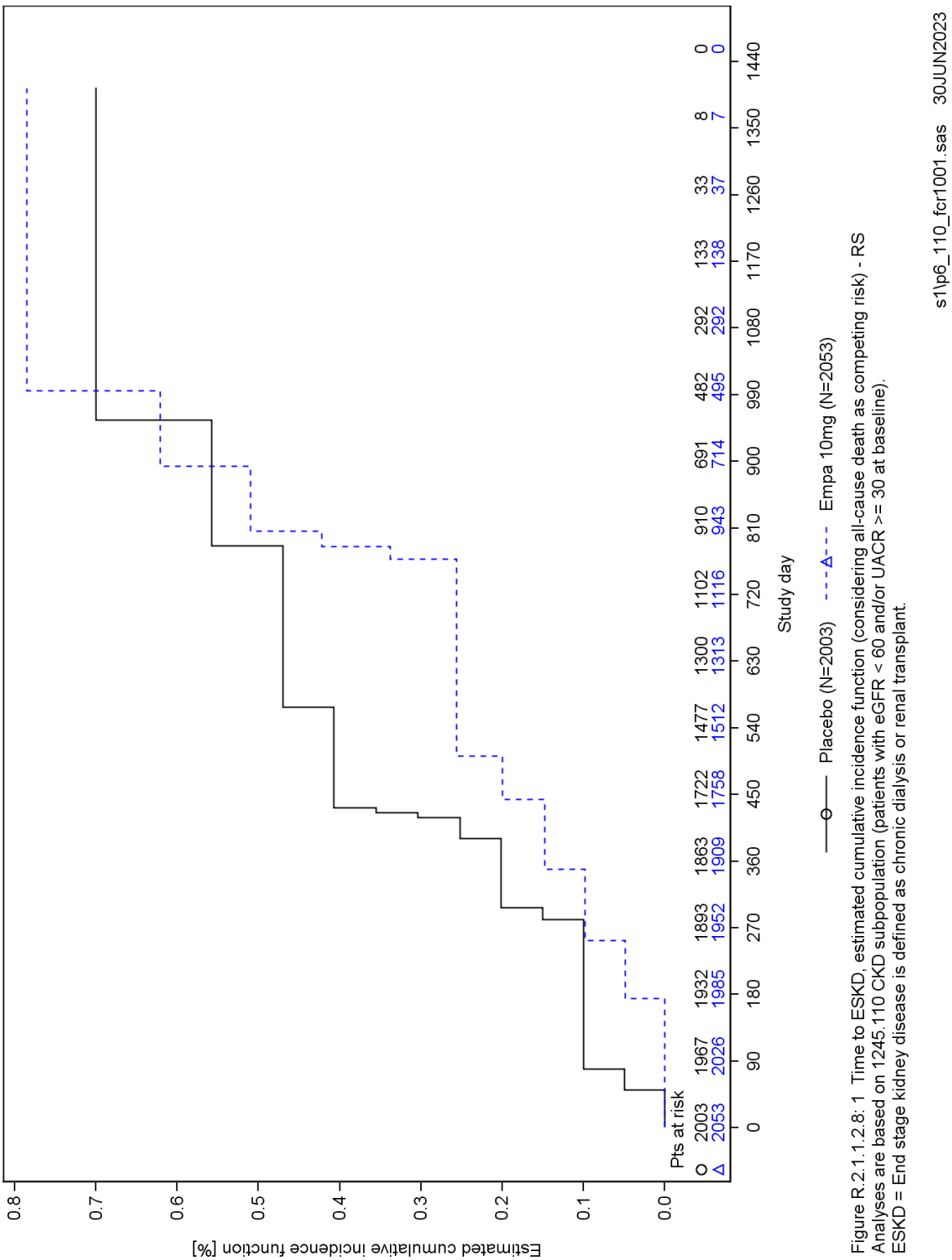


Figure R.2.1.1.2.8: 1 Time to ESKD, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

R.2.1.1.2.9 Time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death

Table R.2.1.1.2.9: 1 Cox Regression for time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 24 | 1.2 | 0.72 | 2053 | 21 | 1.0 | 0.61 | 0.75 | (0.41, 1.36) | 0.3393 | |
| Sex | | | | | | | | | | | | 0.6907 |
| Male | 1065 | 16 | 1.5 | 0.90 | 1094 | 16 | 1.5 | 0.87 | 0.81 | (0.40, 1.63) | 0.5528 | |
| Female | 938 | 8 | 0.9 | 0.51 | 959 | 5 | 0.5 | 0.31 | 0.62 | (0.20, 1.90) | 0.4000 | |
| Age [years] | | | | | | | | | | | | 0.6840 |
| <65 | 331 | 9 | 2.7 | 1.60 | 313 | 9 | 2.9 | 1.71 | 0.94 | (0.37, 2.37) | 0.8897 | |
| >=65 | 1672 | 15 | 0.9 | 0.54 | 1740 | 12 | 0.7 | 0.41 | 0.73 | (0.34, 1.57) | 0.4184 | |
| Region | | | | | | | | | | | | 0.9541 |
| North America | 273 | 7 | 2.6 | 1.55 | 274 | 7 | 2.6 | 1.55 | 0.82 | (0.29, 2.36) | 0.7172 | |
| Latin America | 511 | 9 | 1.8 | 1.16 | 504 | 8 | 1.6 | 1.03 | 0.81 | (0.31, 2.12) | 0.6647 | |
| Europe | 867 | 3 | 0.3 | 0.20 | 894 | 3 | 0.3 | 0.19 | 0.89 | (0.18, 4.41) | 0.8850 | |
| Asia | 231 | 2 | 0.9 | 0.48 | 248 | 2 | 0.8 | 0.44 | 0.64 | (0.09, 4.58) | 0.6556 | |
| Other | 121 | 3 | 2.5 | 1.51 | 133 | 1 | 0.8 | 0.49 | 0.32 | (0.03, 3.06) | 0.3203 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1022 |
| Diabetic | 1046 | 17 | 1.6 | 0.99 | 1082 | 20 | 1.8 | 1.11 | 0.98 | (0.51, 1.88) | 0.9452 | |
| Non-Diabetic | 957 | 7 | 0.7 | 0.43 | 971 | 1 | 0.1 | 0.06 | 0.16 | (0.02, 1.27) | 0.0827 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.6292 |
| <30 | 1087 | 12 | 1.1 | 0.68 | 1094 | 8 | 0.7 | 0.44 | 0.64 | (0.26, 1.57) | 0.3268 | |
| >=30 | 916 | 12 | 1.3 | 0.77 | 959 | 13 | 1.4 | 0.80 | 0.86 | (0.39, 1.89) | 0.7009 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1352 |
| <130 | 827 | 9 | 1.1 | 0.66 | 853 | 3 | 0.4 | 0.21 | 0.31 | (0.08, 1.17) | 0.0839 | |
| >=130 | 1176 | 15 | 1.3 | 0.76 | 1200 | 18 | 1.5 | 0.89 | 0.98 | (0.49, 1.96) | 0.9470 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2536 |
| <75 | 936 | 10 | 1.1 | 0.65 | 935 | 12 | 1.3 | 0.77 | 1.10 | (0.47, 2.57) | 0.8186 | |
| 75 to <85 | 658 | 8 | 1.2 | 0.72 | 703 | 2 | 0.3 | 0.17 | 0.25 | (0.05, 1.19) | 0.0814 | |
| >=85 | 409 | 6 | 1.5 | 0.89 | 415 | 7 | 1.7 | 1.00 | 0.67 | (0.22, 2.10) | 0.4978 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

Table R.2.1.1.2.9: 1 Cox Regression for time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.9549 |
| <30 | 161 | 10 | 6.2 | 4.38 | 148 | 9 | 6.1 | 4.04 | 0.68 | (0.27, 1.70) | 0.4090 | |
| 30 to <45 | 550 | 9 | 1.6 | 0.98 | 564 | 8 | 1.4 | 0.86 | 0.82 | (0.31, 2.13) | 0.6820 | |
| >=45 | 1291 | 5 | 0.4 | 0.23 | 1341 | 4 | 0.3 | 0.18 | 0.82 | (0.22, 3.04) | 0.7618 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.5072 |
| Normal (<30) | 766 | 1 | 0.1 | 0.08 | 787 | 2 | 0.3 | 0.15 | 2.10 | (0.19,23.24) | 0.5436 | |
| Microalbuminuria (30 to <=300) | 921 | 9 | 1.0 | 0.58 | 939 | 5 | 0.5 | 0.32 | 0.49 | (0.16, 1.48) | 0.2066 | |
| Macroalbuminuria (>300) | 311 | 14 | 4.5 | 2.86 | 318 | 14 | 4.4 | 2.77 | 0.84 | (0.39, 1.80) | 0.6581 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2695 |
| Low, moderate or high | 1479 | 3 | 0.2 | 0.12 | 1549 | 5 | 0.3 | 0.19 | 1.68 | (0.40, 7.05) | 0.4756 | |
| Very high | 519 | 21 | 4.0 | 2.58 | 495 | 16 | 3.2 | 2.07 | 0.69 | (0.36, 1.34) | 0.2736 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.8030 |
| No | 412 | 7 | 1.7 | 1.08 | 411 | 6 | 1.5 | 0.87 | 0.85 | (0.28, 2.57) | 0.7732 | |
| Yes | 1591 | 17 | 1.1 | 0.63 | 1642 | 15 | 0.9 | 0.55 | 0.72 | (0.35, 1.46) | 0.3624 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5653 |
| No | 282 | 3 | 1.1 | 0.66 | 277 | 3 | 1.1 | 0.70 | 1.17 | (0.23, 5.86) | 0.8482 | |
| Yes | 1721 | 21 | 1.2 | 0.73 | 1776 | 18 | 1.0 | 0.60 | 0.70 | (0.37, 1.33) | 0.2820 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9885 |
| No | 229 | 1 | 0.4 | 0.25 | 250 | 0 | 0 | 0.00 | <0.01 | | 0.9883 | |
| Yes | 1774 | 23 | 1.3 | 0.78 | 1803 | 21 | 1.2 | 0.70 | 0.78 | (0.43, 1.42) | 0.4084 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.2.1.1.2.9: 1**

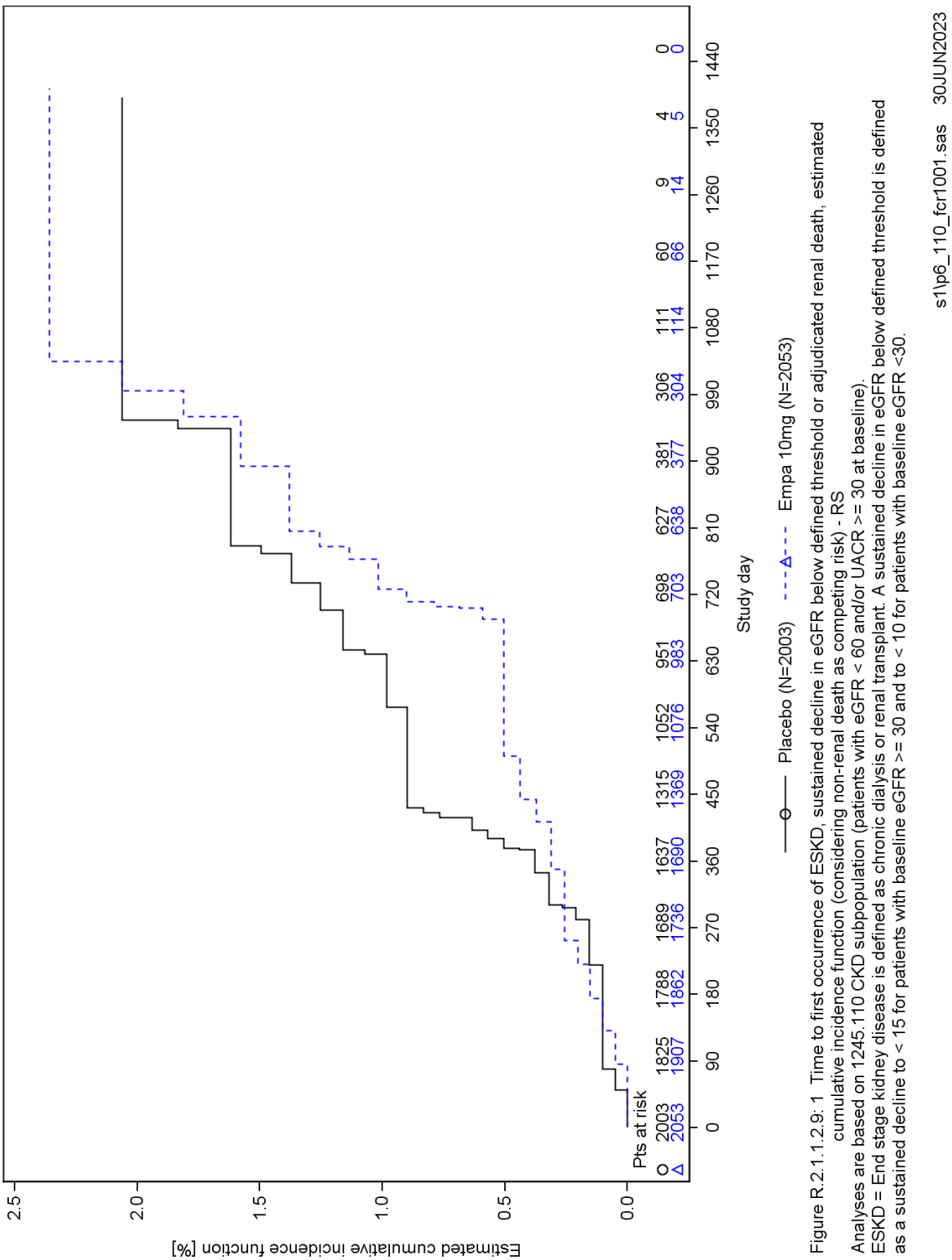


Figure R.2.1.1.2.9: 1 Time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death, estimated cumulative incidence function (considering non-renal death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

R.2.1.1.2.10 Time to first occurrence of ESKD or sustained decline in eGFR below defined threshold

Table R.2.1.1.2.10: 1 Cox Regression for time to first occurrence of ESKD or a sustained decline in eGFR below defined threshold until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 16 | 0.8 | 0.48 | 2053 | 19 | 0.9 | 0.55 | 0.97 | (0.49, 1.90) | 0.9211 | |
| Sex | | | | | | | | | | | | 0.1315 |
| Male | 1065 | 8 | 0.8 | 0.45 | 1094 | 15 | 1.4 | 0.82 | 1.44 | (0.60, 3.45) | 0.4089 | |
| Female | 938 | 8 | 0.9 | 0.51 | 959 | 4 | 0.4 | 0.25 | 0.46 | (0.14, 1.54) | 0.2056 | |
| Age [years] | | | | | | | | | | | | 0.6596 |
| <65 | 331 | 5 | 1.5 | 0.89 | 313 | 7 | 2.2 | 1.33 | 1.27 | (0.40, 4.04) | 0.6812 | |
| >=65 | 1672 | 11 | 0.7 | 0.40 | 1740 | 12 | 0.7 | 0.41 | 0.93 | (0.41, 2.12) | 0.8556 | |
| Region | | | | | | | | | | | | 0.9747 |
| North America | 273 | 6 | 2.2 | 1.33 | 274 | 6 | 2.2 | 1.33 | 0.81 | (0.26, 2.52) | 0.7099 | |
| Latin America | 511 | 5 | 1.0 | 0.65 | 504 | 8 | 1.6 | 1.03 | 1.37 | (0.44, 4.24) | 0.5861 | |
| Europe | 867 | 3 | 0.3 | 0.20 | 894 | 3 | 0.3 | 0.19 | 0.86 | (0.17, 4.28) | 0.8558 | |
| Asia | 231 | 1 | 0.4 | 0.24 | 248 | 2 | 0.8 | 0.44 | 1.20 | (0.11,13.41) | 0.8813 | |
| Other | 121 | 1 | 0.8 | 0.51 | 133 | 0 | 0 | 0.00 | <0.01 | | 0.9868 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2178 |
| Diabetic | 1046 | 12 | 1.1 | 0.70 | 1082 | 18 | 1.7 | 1.00 | 1.17 | (0.56, 2.46) | 0.6778 | |
| Non-Diabetic | 957 | 4 | 0.4 | 0.25 | 971 | 1 | 0.1 | 0.06 | 0.27 | (0.03, 2.45) | 0.2452 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9019 |
| <30 | 1087 | 7 | 0.6 | 0.40 | 1094 | 8 | 0.7 | 0.44 | 1.02 | (0.37, 2.83) | 0.9711 | |
| >=30 | 916 | 9 | 1.0 | 0.58 | 959 | 11 | 1.1 | 0.68 | 0.94 | (0.38, 2.28) | 0.8847 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5218 |
| <130 | 827 | 3 | 0.4 | 0.22 | 853 | 2 | 0.2 | 0.14 | 0.57 | (0.09, 3.43) | 0.5365 | |
| >=130 | 1176 | 13 | 1.1 | 0.66 | 1200 | 17 | 1.4 | 0.84 | 1.07 | (0.51, 2.24) | 0.8550 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2619 |
| <75 | 936 | 6 | 0.6 | 0.39 | 935 | 11 | 1.2 | 0.71 | 1.60 | (0.59, 4.35) | 0.3606 | |
| 75 to <85 | 658 | 6 | 0.9 | 0.54 | 703 | 2 | 0.3 | 0.17 | 0.35 | (0.07, 1.73) | 0.1974 | |
| >=85 | 409 | 4 | 1.0 | 0.60 | 415 | 6 | 1.4 | 0.86 | 0.74 | (0.20, 2.75) | 0.6479 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

Table R.2.1.1.2.10: 1 Cox Regression for time to first occurrence of ESKD or a sustained decline in eGFR below defined threshold until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8288 |
| <30 | 161 | 7 | 4.3 | 3.09 | 148 | 9 | 6.1 | 4.04 | 0.96 | (0.35, 2.61) | 0.9380 | |
| 30 to <45 | 550 | 5 | 0.9 | 0.54 | 564 | 7 | 1.2 | 0.75 | 1.31 | (0.41, 4.13) | 0.6498 | |
| >=45 | 1291 | 4 | 0.3 | 0.18 | 1341 | 3 | 0.2 | 0.13 | 0.73 | (0.16, 3.28) | 0.6852 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8079 |
| Normal (<30) | 766 | 0 | 0 | 0.00 | 787 | 1 | 0.1 | 0.07 | >999.99 | | 0.9864 | |
| Microalbuminuria (30 to <=300) | 921 | 6 | 0.7 | 0.39 | 939 | 5 | 0.5 | 0.32 | 0.69 | (0.21, 2.28) | 0.5378 | |
| Macroalbuminuria (>300) | 311 | 10 | 3.2 | 2.05 | 318 | 13 | 4.1 | 2.57 | 1.12 | (0.48, 2.62) | 0.7937 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3595 |
| Low, moderate or high | 1479 | 1 | 0.1 | 0.04 | 1549 | 3 | 0.2 | 0.11 | 2.94 | (0.31,28.25) | 0.3510 | |
| Very high | 519 | 15 | 2.9 | 1.85 | 495 | 16 | 3.2 | 2.07 | 0.97 | (0.48, 1.97) | 0.9307 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6815 |
| No | 412 | 5 | 1.2 | 0.77 | 411 | 6 | 1.5 | 0.87 | 1.22 | (0.36, 4.09) | 0.7516 | |
| Yes | 1591 | 11 | 0.7 | 0.41 | 1642 | 13 | 0.8 | 0.47 | 0.89 | (0.39, 2.03) | 0.7856 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4616 |
| No | 282 | 1 | 0.4 | 0.22 | 277 | 2 | 0.7 | 0.47 | 2.28 | (0.20,25.50) | 0.5039 | |
| Yes | 1721 | 15 | 0.9 | 0.52 | 1776 | 17 | 1.0 | 0.57 | 0.89 | (0.44, 1.79) | 0.7347 | |
| Baseline use of diuretics | | | | | | | | | | | | 1.0000 |
| No | 229 | 0 | 0 | 0.00 | 250 | 0 | 0 | 0.00 | 0.99 | | 1.0000 | |
| Yes | 1774 | 16 | 0.9 | 0.55 | 1803 | 19 | 1.1 | 0.63 | 0.95 | (0.48, 1.86) | 0.8771 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.2.1.1.2.10: 1**

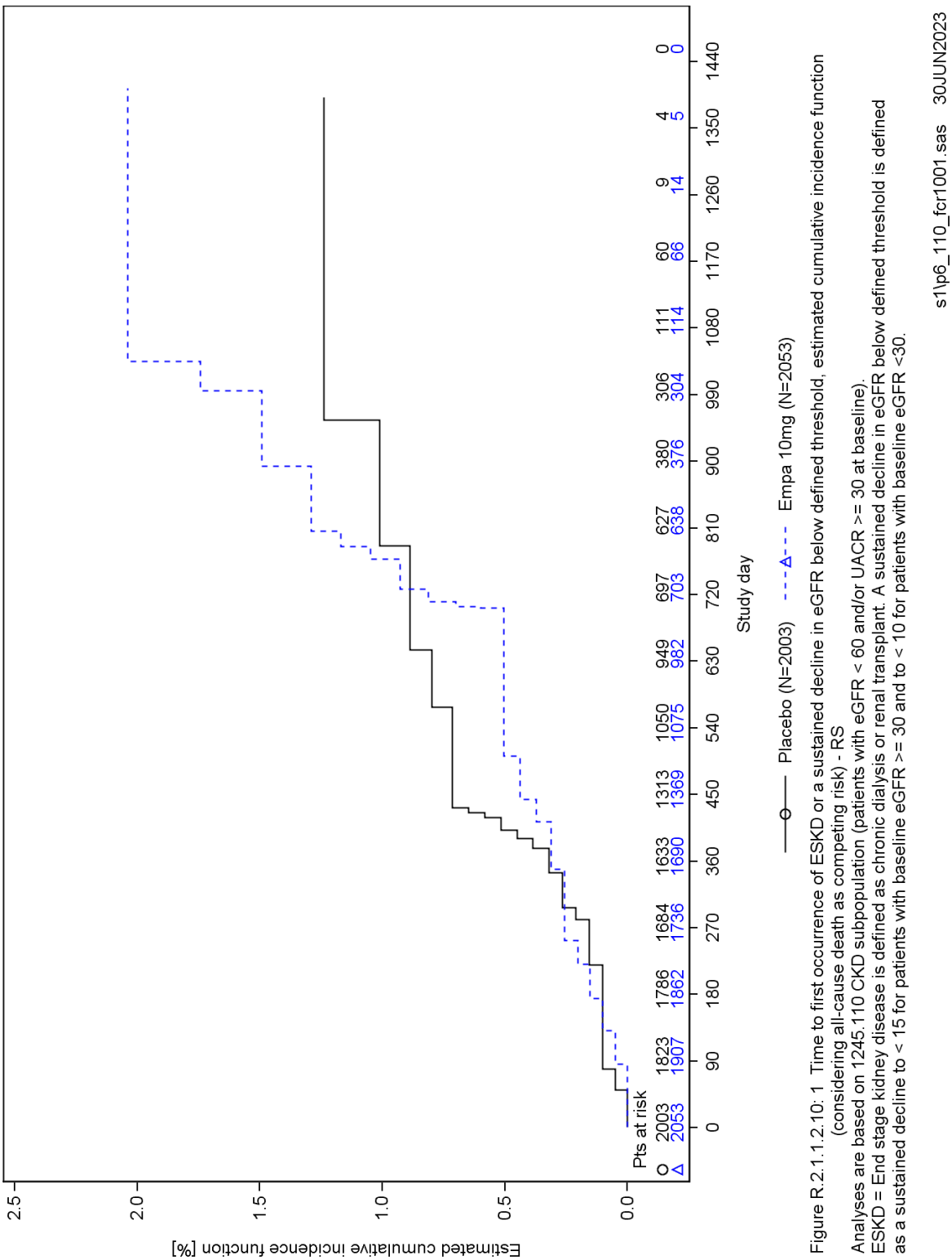


Figure R.2.1.1.2.10: 1 Time to first occurrence of ESKD or a sustained decline in eGFR below defined threshold, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

R.2.1.1.2.11 Time to first occurrence of sustained decline in eGFR below defined threshold

Table R.2.1.1.2.11: 1 Cox Regression for time to first occurrence of a sustained decline in eGFR below defined threshold until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2003 | 8 | 0.4 | 0.24 | 2053 | 10 | 0.5 | 0.29 | 1.01 | (0.39,2.63) | 0.9756 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.2.1.1.2.11: 1**

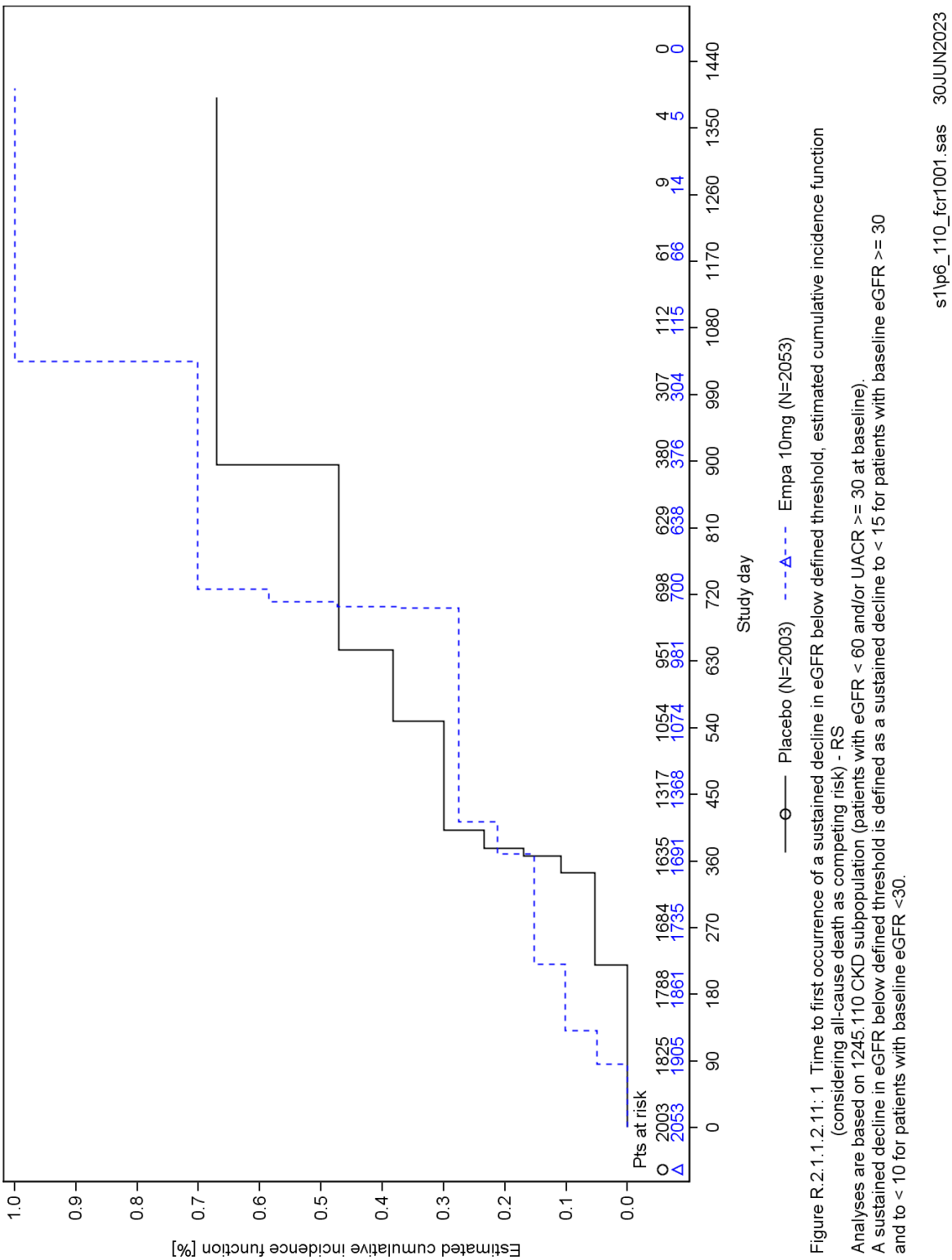


Figure R.2.1.1.2.11: 1 Time to first occurrence of a sustained decline in eGFR below defined threshold, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

R.2.1.1.2.12 Time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2

Table R.2.1.1.2.12: 1 Cox Regression for time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2 until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 24 | 1.2 | 0.72 | 2053 | 22 | 1.1 | 0.64 | 0.74 | (0.41, 1.34) | 0.3216 | |
| Sex | | | | | | | | | | | | 0.1355 |
| Male | 1065 | 14 | 1.3 | 0.79 | 1094 | 18 | 1.6 | 0.98 | 1.01 | (0.49, 2.06) | 0.9796 | |
| Female | 938 | 10 | 1.1 | 0.64 | 959 | 4 | 0.4 | 0.25 | 0.35 | (0.11, 1.14) | 0.0825 | |
| Age [years] | | | | | | | | | | | | 0.3594 |
| <65 | 331 | 8 | 2.4 | 1.43 | 313 | 9 | 2.9 | 1.73 | 1.14 | (0.43, 2.97) | 0.7938 | |
| >=65 | 1672 | 16 | 1.0 | 0.58 | 1740 | 13 | 0.7 | 0.45 | 0.64 | (0.31, 1.36) | 0.2457 | |
| Region | | | | | | | | | | | | 0.9768 |
| North America | 273 | 8 | 2.9 | 1.78 | 274 | 6 | 2.2 | 1.33 | 0.63 | (0.22, 1.82) | 0.3944 | |
| Latin America | 511 | 9 | 1.8 | 1.17 | 504 | 9 | 1.8 | 1.16 | 0.91 | (0.35, 2.33) | 0.8422 | |
| Europe | 867 | 3 | 0.3 | 0.20 | 894 | 4 | 0.4 | 0.26 | 1.12 | (0.25, 5.02) | 0.8824 | |
| Asia | 231 | 2 | 0.9 | 0.48 | 248 | 3 | 1.2 | 0.66 | 0.72 | (0.12, 4.44) | 0.7272 | |
| Other | 121 | 2 | 1.7 | 1.03 | 133 | 0 | 0 | 0.00 | <0.01 | | 0.9819 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3635 |
| Diabetic | 1046 | 18 | 1.7 | 1.05 | 1082 | 20 | 1.8 | 1.12 | 0.85 | (0.44, 1.62) | 0.6203 | |
| Non-Diabetic | 957 | 6 | 0.6 | 0.37 | 971 | 2 | 0.2 | 0.12 | 0.38 | (0.08, 1.90) | 0.2375 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9259 |
| <30 | 1087 | 10 | 0.9 | 0.57 | 1094 | 9 | 0.8 | 0.50 | 0.72 | (0.29, 1.79) | 0.4776 | |
| >=30 | 916 | 14 | 1.5 | 0.90 | 959 | 13 | 1.4 | 0.80 | 0.76 | (0.35, 1.63) | 0.4822 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.2678 |
| <130 | 827 | 5 | 0.6 | 0.37 | 853 | 2 | 0.2 | 0.14 | 0.32 | (0.06, 1.68) | 0.1796 | |
| >=130 | 1176 | 19 | 1.6 | 0.97 | 1200 | 20 | 1.7 | 0.99 | 0.88 | (0.46, 1.68) | 0.7040 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2463 |
| <75 | 936 | 9 | 1.0 | 0.58 | 935 | 12 | 1.3 | 0.77 | 1.09 | (0.46, 2.62) | 0.8385 | |
| 75 to <85 | 658 | 8 | 1.2 | 0.72 | 703 | 2 | 0.3 | 0.17 | 0.25 | (0.05, 1.20) | 0.0834 | |
| >=85 | 409 | 7 | 1.7 | 1.05 | 415 | 8 | 1.9 | 1.15 | 0.58 | (0.20, 1.65) | 0.3038 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

Table R.2.1.1.2.12: 1 Cox Regression for time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2 until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6158 |
| <30 | 161 | 15 | 9.3 | 6.78 | 148 | 12 | 8.1 | 5.52 | 0.64 | (0.30, 1.39) | 0.2616 | |
| 30 to <45 | 550 | 5 | 0.9 | 0.54 | 564 | 7 | 1.2 | 0.75 | 1.28 | (0.41, 4.06) | 0.6702 | |
| >=45 | 1291 | 4 | 0.3 | 0.18 | 1341 | 3 | 0.2 | 0.13 | 0.74 | (0.17, 3.31) | 0.6941 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9670 |
| Normal (<30) | 766 | 0 | 0 | 0.00 | 787 | 1 | 0.1 | 0.07 | >999.99 | | 0.9871 | |
| Microalbuminuria (30 to <=300) | 921 | 6 | 0.7 | 0.39 | 939 | 5 | 0.5 | 0.32 | 0.64 | (0.19, 2.14) | 0.4732 | |
| Macroalbuminuria (>300) | 311 | 18 | 5.8 | 3.74 | 318 | 16 | 5.0 | 3.20 | 0.77 | (0.39, 1.55) | 0.4717 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2558 |
| Low, moderate or high | 1479 | 1 | 0.1 | 0.04 | 1549 | 3 | 0.2 | 0.11 | 2.95 | (0.31,28.35) | 0.3493 | |
| Very high | 519 | 23 | 4.4 | 2.85 | 495 | 19 | 3.8 | 2.47 | 0.76 | (0.41, 1.39) | 0.3721 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9934 |
| No | 412 | 8 | 1.9 | 1.24 | 411 | 6 | 1.5 | 0.87 | 0.75 | (0.25, 2.24) | 0.6076 | |
| Yes | 1591 | 16 | 1.0 | 0.60 | 1642 | 16 | 1.0 | 0.58 | 0.75 | (0.37, 1.52) | 0.4221 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.0759 |
| No | 282 | 1 | 0.4 | 0.22 | 277 | 4 | 1.4 | 0.94 | 4.79 | (0.53,43.46) | 0.1634 | |
| Yes | 1721 | 23 | 1.3 | 0.80 | 1776 | 18 | 1.0 | 0.60 | 0.60 | (0.32, 1.12) | 0.1113 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9462 |
| No | 229 | 1 | 0.4 | 0.25 | 250 | 1 | 0.4 | 0.24 | 0.68 | (0.04,11.53) | 0.7876 | |
| Yes | 1774 | 23 | 1.3 | 0.79 | 1803 | 21 | 1.2 | 0.70 | 0.75 | (0.41, 1.36) | 0.3434 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

**Figure R.2.1.1.2.12: 1**

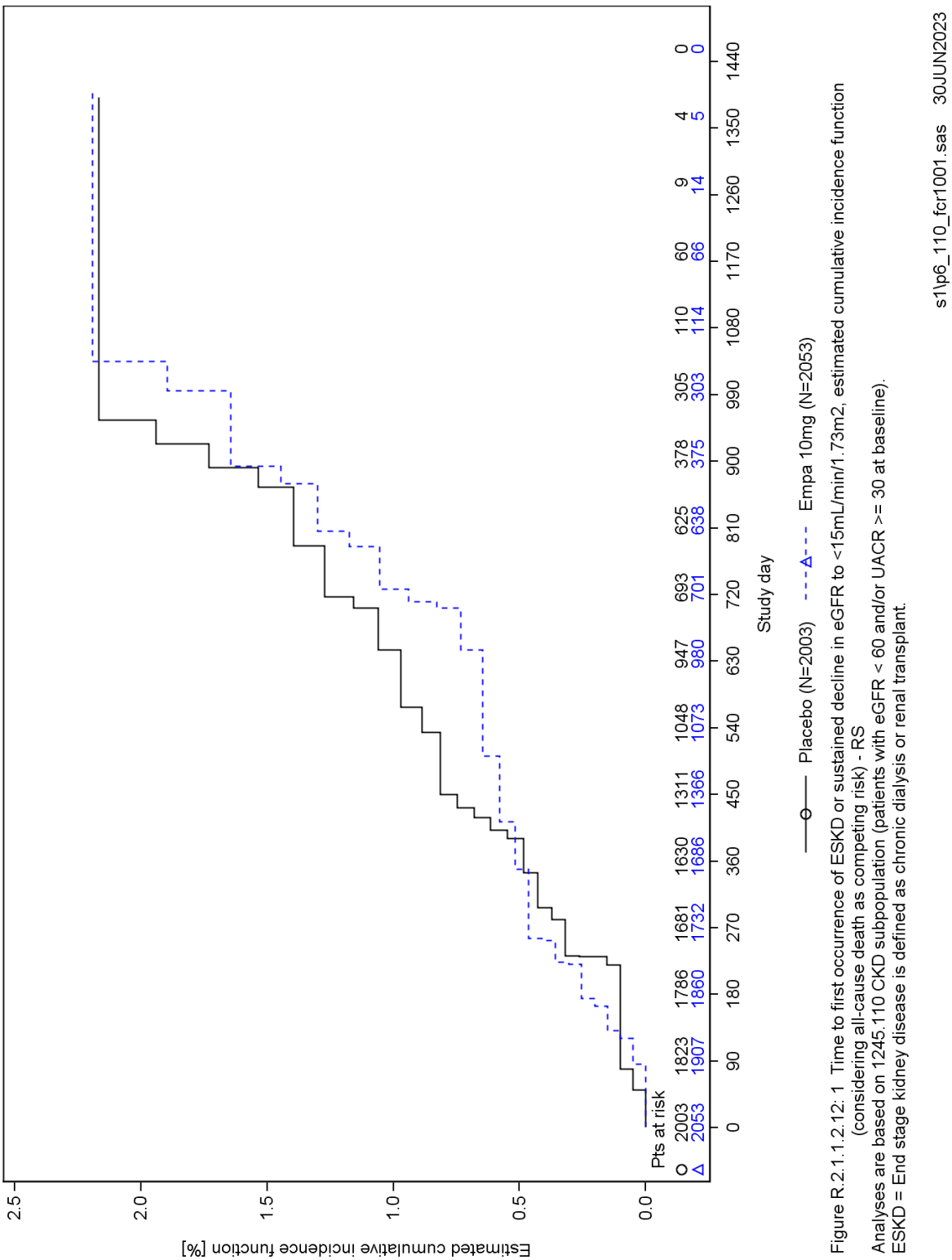


Figure R.2.1.1.2.12: 1 Time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

R.2.1.1.2.13 Time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2

Table R.2.1.1.2.13: 1 Cox Regression for time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2 until the end of planned treatment period overall - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 18 | 0.9 | 0.54 | 2053 | 15 | 0.7 | 0.44 | 0.69 | (0.34,1.40) | 0.3019 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.2.13: 1**

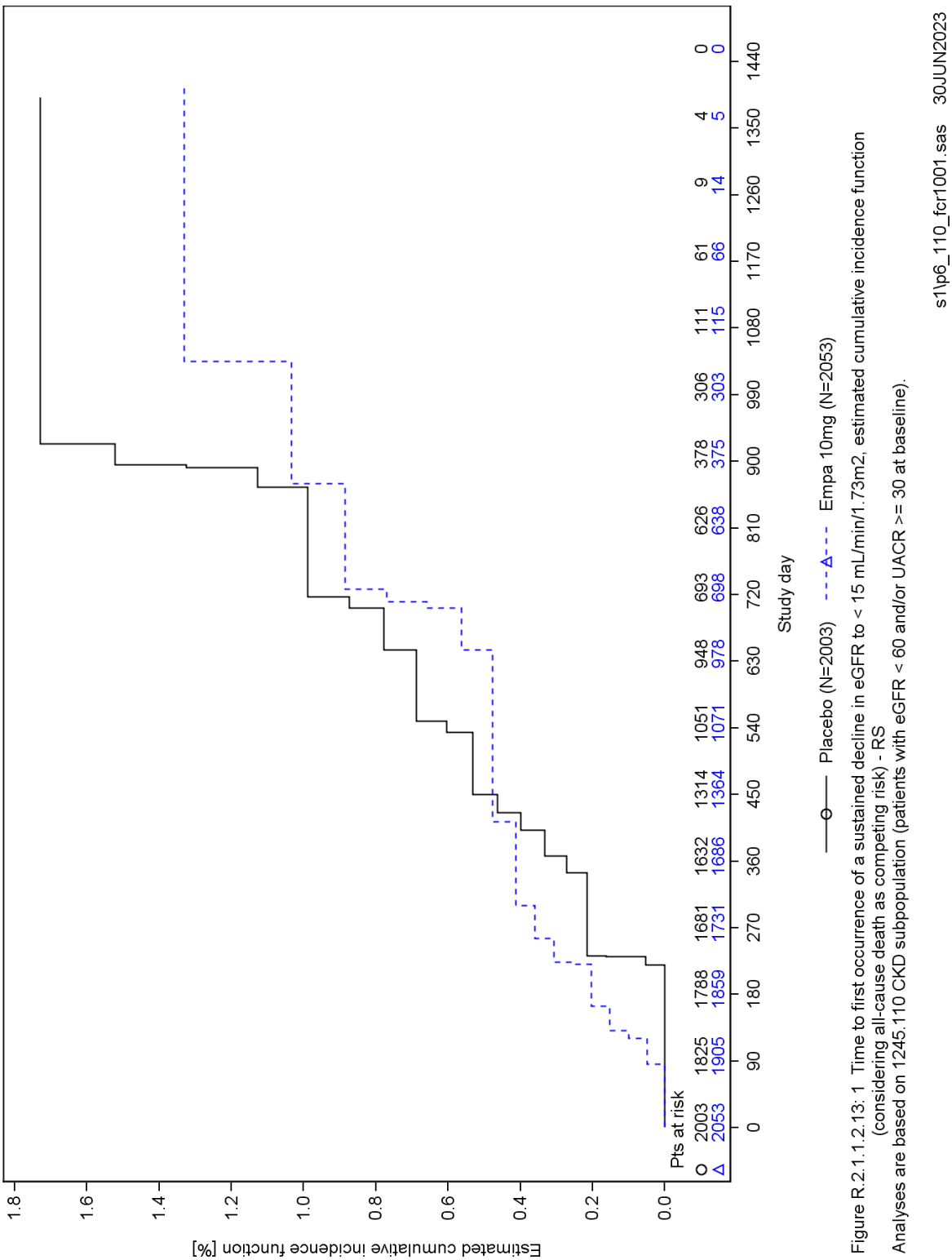


Figure R.2.1.1.2.13: 1 Time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.2.1.1.2.14**

R.2.1.1.2.14 Time to first occurrence of acute kidney injury

Table R.2.1.1.2.14: 1 Cox Regression for time to first occurrence of acute kidney injury until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 113 | 5.6 | 2.78 | 2053 | 87 | 4.2 | 2.08 | 0.75 | (0.57,0.99) | 0.0449 | |
| Sex | | | | | | | | | | | | 0.2638 |
| Male | 1065 | 63 | 5.9 | 2.95 | 1094 | 44 | 4.0 | 1.98 | 0.65 | (0.44,0.95) | 0.0268 | |
| Female | 938 | 50 | 5.3 | 2.60 | 959 | 43 | 4.5 | 2.20 | 0.89 | (0.59,1.34) | 0.5800 | |
| Age [years] | | | | | | | | | | | | 0.4438 |
| <65 | 331 | 14 | 4.2 | 2.05 | 313 | 13 | 4.2 | 2.04 | 0.99 | (0.46,2.10) | 0.9704 | |
| >=65 | 1672 | 99 | 5.9 | 2.93 | 1740 | 74 | 4.3 | 2.09 | 0.72 | (0.53,0.97) | 0.0309 | |
| Region | | | | | | | | | | | | 0.5124 |
| North America | 273 | 42 | 15.4 | 7.69 | 274 | 38 | 13.9 | 6.84 | 0.88 | (0.57,1.37) | 0.5820 | |
| Latin America | 511 | 21 | 4.1 | 2.13 | 504 | 17 | 3.4 | 1.74 | 0.81 | (0.43,1.53) | 0.5123 | |
| Europe | 867 | 31 | 3.6 | 1.71 | 894 | 18 | 2.0 | 0.96 | 0.56 | (0.31,1.00) | 0.0489 | |
| Asia | 231 | 9 | 3.9 | 1.88 | 248 | 4 | 1.6 | 0.76 | 0.39 | (0.12,1.27) | 0.1178 | |
| Other | 121 | 10 | 8.3 | 4.16 | 133 | 10 | 7.5 | 4.04 | 1.03 | (0.43,2.49) | 0.9400 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.4826 |
| Diabetic | 1046 | 74 | 7.1 | 3.52 | 1082 | 54 | 5.0 | 2.47 | 0.70 | (0.49,0.99) | 0.0439 | |
| Non-Diabetic | 957 | 39 | 4.1 | 1.99 | 971 | 33 | 3.4 | 1.66 | 0.86 | (0.54,1.37) | 0.5194 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0990 |
| <30 | 1087 | 55 | 5.1 | 2.55 | 1094 | 32 | 2.9 | 1.45 | 0.57 | (0.37,0.88) | 0.0115 | |
| >=30 | 916 | 58 | 6.3 | 3.04 | 959 | 55 | 5.7 | 2.79 | 0.92 | (0.64,1.33) | 0.6660 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.4336 |
| <130 | 827 | 53 | 6.4 | 3.23 | 853 | 47 | 5.5 | 2.74 | 0.83 | (0.56,1.24) | 0.3702 | |
| >=130 | 1176 | 60 | 5.1 | 2.48 | 1200 | 40 | 3.3 | 1.62 | 0.67 | (0.45,1.00) | 0.0474 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2637 |
| <75 | 936 | 66 | 7.1 | 3.50 | 935 | 55 | 5.9 | 2.92 | 0.82 | (0.57,1.17) | 0.2663 | |
| 75 to <85 | 658 | 28 | 4.3 | 2.07 | 703 | 24 | 3.4 | 1.68 | 0.85 | (0.49,1.46) | 0.5521 | |
| >=85 | 409 | 19 | 4.6 | 2.30 | 415 | 8 | 1.9 | 0.92 | 0.40 | (0.17,0.91) | 0.0287 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

Table R.2.1.1.2.14: 1 Cox Regression for time to first occurrence of acute kidney injury until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6317 |
| <30 | 161 | 19 | 11.8 | 6.72 | 148 | 17 | 11.5 | 6.03 | 0.93 | (0.48,1.80) | 0.8282 | |
| 30 to <45 | 550 | 40 | 7.3 | 3.58 | 564 | 32 | 5.7 | 2.84 | 0.83 | (0.52,1.32) | 0.4254 | |
| >=45 | 1291 | 54 | 4.2 | 2.03 | 1341 | 38 | 2.8 | 1.37 | 0.66 | (0.44,1.00) | 0.0508 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.6663 |
| Normal (<30) | 766 | 34 | 4.4 | 2.15 | 787 | 28 | 3.6 | 1.72 | 0.89 | (0.54,1.47) | 0.6588 | |
| Microalbuminuria (30 to <=300) | 921 | 57 | 6.2 | 3.07 | 939 | 43 | 4.6 | 2.25 | 0.67 | (0.45,0.99) | 0.0447 | |
| Macroalbuminuria (>300) | 311 | 22 | 7.1 | 3.58 | 318 | 16 | 5.0 | 2.58 | 0.73 | (0.38,1.40) | 0.3472 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.8853 |
| Low, moderate or high | 1479 | 64 | 4.3 | 2.10 | 1549 | 49 | 3.2 | 1.53 | 0.74 | (0.51,1.08) | 0.1171 | |
| Very high | 519 | 49 | 9.4 | 4.87 | 495 | 38 | 7.7 | 3.99 | 0.77 | (0.51,1.18) | 0.2381 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9575 |
| No | 412 | 26 | 6.3 | 3.17 | 411 | 19 | 4.6 | 2.25 | 0.76 | (0.42,1.37) | 0.3632 | |
| Yes | 1591 | 87 | 5.5 | 2.68 | 1642 | 68 | 4.1 | 2.04 | 0.75 | (0.54,1.02) | 0.0704 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5727 |
| No | 282 | 18 | 6.4 | 3.26 | 277 | 11 | 4.0 | 2.07 | 0.61 | (0.29,1.30) | 0.2051 | |
| Yes | 1721 | 95 | 5.5 | 2.71 | 1776 | 76 | 4.3 | 2.08 | 0.78 | (0.57,1.05) | 0.1009 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.1486 |
| No | 229 | 11 | 4.8 | 2.30 | 250 | 4 | 1.6 | 0.79 | 0.33 | (0.11,1.05) | 0.0609 | |
| Yes | 1774 | 102 | 5.7 | 2.85 | 1803 | 83 | 4.6 | 2.26 | 0.80 | (0.60,1.07) | 0.1297 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

**Figure R.2.1.1.2.14: 1**

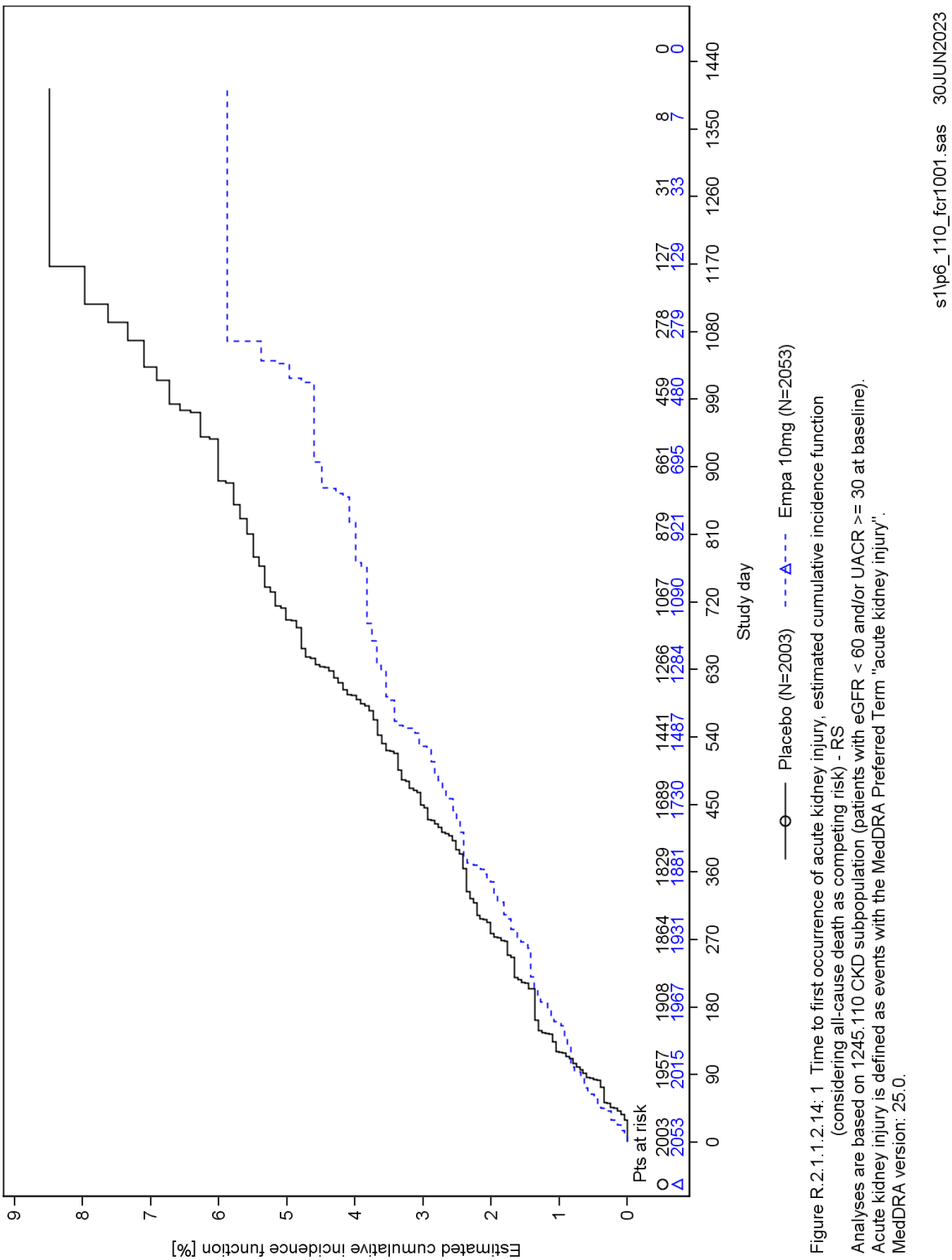


Figure R.2.1.1.2.14: 1 Time to first occurrence of acute kidney injury, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

**R.2.1.1.3**

R.2.1.1.3.1 Time to first occurrence of an adjudicated major cardiovascular event

Table R.2.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 467 | 23.3 | 12.48 | 2053 | 412 | 20.1 | 10.43 | 0.83 | (0.73,0.95) | 0.0075 | |
| Sex | | | | | | | | | | | | 0.9659 |
| Male | 1065 | 267 | 25.1 | 13.69 | 1094 | 241 | 22.0 | 11.58 | 0.84 | (0.70,1.00) | 0.0447 | |
| Female | 938 | 200 | 21.3 | 11.16 | 959 | 171 | 17.8 | 9.16 | 0.83 | (0.68,1.02) | 0.0769 | |
| Age [years] | | | | | | | | | | | | 0.4309 |
| <65 | 331 | 67 | 20.2 | 10.66 | 313 | 62 | 19.8 | 10.32 | 0.95 | (0.67,1.34) | 0.7548 | |
| >=65 | 1672 | 400 | 23.9 | 12.84 | 1740 | 350 | 20.1 | 10.46 | 0.81 | (0.71,0.94) | 0.0050 | |
| Region | | | | | | | | | | | | 0.4494 |
| North America | 273 | 82 | 30.0 | 16.31 | 274 | 71 | 25.9 | 13.41 | 0.81 | (0.59,1.11) | 0.1867 | |
| Latin America | 511 | 109 | 21.3 | 11.71 | 504 | 110 | 21.8 | 11.92 | 1.02 | (0.78,1.33) | 0.8830 | |
| Europe | 867 | 181 | 20.9 | 10.83 | 894 | 146 | 16.3 | 8.21 | 0.76 | (0.61,0.94) | 0.0130 | |
| Asia | 231 | 61 | 26.4 | 14.50 | 248 | 52 | 21.0 | 10.78 | 0.73 | (0.50,1.06) | 0.0951 | |
| Other | 121 | 34 | 28.1 | 15.67 | 133 | 33 | 24.8 | 14.07 | 0.93 | (0.58,1.50) | 0.7696 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3766 |
| Diabetic | 1046 | 276 | 26.4 | 14.51 | 1082 | 237 | 21.9 | 11.60 | 0.79 | (0.67,0.94) | 0.0092 | |
| Non-Diabetic | 957 | 191 | 20.0 | 10.37 | 971 | 175 | 18.0 | 9.18 | 0.90 | (0.73,1.10) | 0.2960 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2148 |
| <30 | 1087 | 277 | 25.5 | 14.07 | 1094 | 225 | 20.6 | 10.81 | 0.78 | (0.65,0.93) | 0.0049 | |
| >=30 | 916 | 190 | 20.7 | 10.71 | 959 | 187 | 19.5 | 10.01 | 0.92 | (0.75,1.13) | 0.4191 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8414 |
| <130 | 827 | 191 | 23.1 | 12.74 | 853 | 173 | 20.3 | 10.59 | 0.82 | (0.67,1.01) | 0.0614 | |
| >=130 | 1176 | 276 | 23.5 | 12.30 | 1200 | 239 | 19.9 | 10.32 | 0.84 | (0.71,1.00) | 0.0557 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2946 |
| <75 | 936 | 231 | 24.7 | 13.34 | 935 | 212 | 22.7 | 11.86 | 0.88 | (0.73,1.06) | 0.1796 | |
| 75 to <85 | 658 | 155 | 23.6 | 12.46 | 703 | 120 | 17.1 | 8.86 | 0.72 | (0.56,0.91) | 0.0061 | |
| >=85 | 409 | 81 | 19.8 | 10.57 | 415 | 80 | 19.3 | 9.91 | 0.94 | (0.69,1.28) | 0.6889 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.

Table R.2.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8277 |
| <30 | 161 | 58 | 36.0 | 22.91 | 148 | 50 | 33.8 | 19.82 | 0.89 | (0.61,1.30) | 0.5336 | |
| 30 to <45 | 550 | 139 | 25.3 | 13.81 | 564 | 127 | 22.5 | 11.93 | 0.88 | (0.69,1.11) | 0.2817 | |
| >=45 | 1291 | 270 | 20.9 | 10.88 | 1341 | 235 | 17.5 | 8.93 | 0.81 | (0.68,0.96) | 0.0170 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9552 |
| Normal (<30) | 766 | 138 | 18.0 | 9.34 | 787 | 122 | 15.5 | 7.77 | 0.85 | (0.67,1.08) | 0.1893 | |
| Microalbuminuria (30 to <=300) | 921 | 218 | 23.7 | 12.68 | 939 | 191 | 20.3 | 10.60 | 0.82 | (0.68,1.00) | 0.0500 | |
| Macroalbuminuria (>300) | 311 | 110 | 35.4 | 20.52 | 318 | 99 | 31.1 | 17.79 | 0.86 | (0.66,1.14) | 0.2948 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.6998 |
| Low, moderate or high | 1479 | 295 | 19.9 | 10.40 | 1549 | 263 | 17.0 | 8.60 | 0.83 | (0.70,0.98) | 0.0262 | |
| Very high | 519 | 171 | 32.9 | 19.10 | 495 | 149 | 30.1 | 17.09 | 0.87 | (0.70,1.09) | 0.2328 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7906 |
| No | 412 | 110 | 26.7 | 14.71 | 411 | 96 | 23.4 | 12.40 | 0.86 | (0.66,1.14) | 0.2927 | |
| Yes | 1591 | 357 | 22.4 | 11.92 | 1642 | 316 | 19.2 | 9.96 | 0.83 | (0.71,0.96) | 0.0143 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5851 |
| No | 282 | 69 | 24.5 | 13.36 | 277 | 60 | 21.7 | 11.70 | 0.91 | (0.65,1.29) | 0.6094 | |
| Yes | 1721 | 398 | 23.1 | 12.34 | 1776 | 352 | 19.8 | 10.25 | 0.82 | (0.71,0.95) | 0.0078 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3479 |
| No | 229 | 44 | 19.2 | 9.58 | 250 | 31 | 12.4 | 6.28 | 0.68 | (0.43,1.07) | 0.0944 | |
| Yes | 1774 | 423 | 23.8 | 12.88 | 1803 | 381 | 21.1 | 11.03 | 0.85 | (0.74,0.98) | 0.0216 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.

**Figure R.2.1.1.3.1: 1**

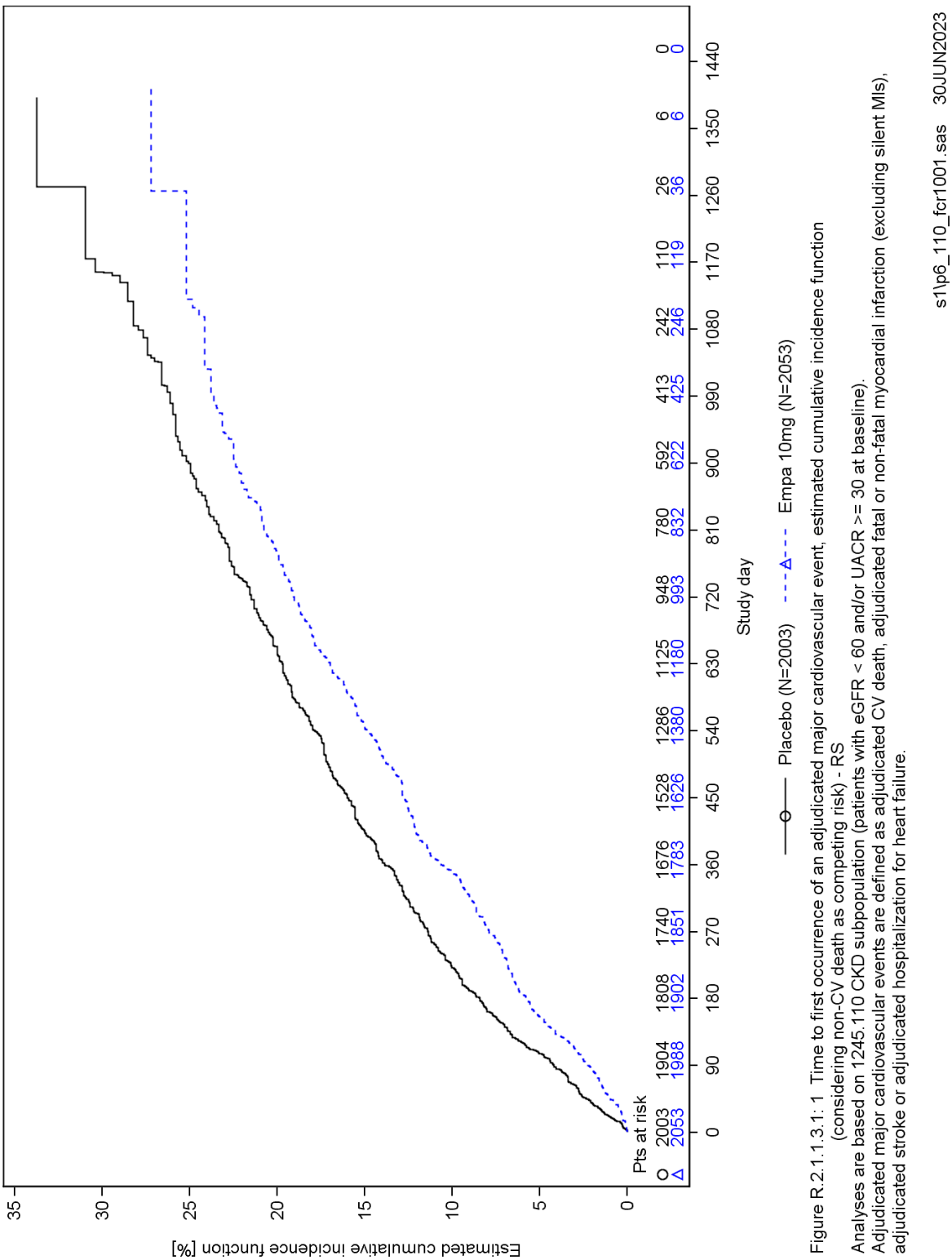


Figure R.2.1.1.3.1: 1 Time to first occurrence of an adjudicated major cardiovascular event, estimated cumulative incidence function (considering non-CV death as competing risk) - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.

R.2.1.1.3.2 Time to first occurrence of an adjudicated myocardial infarction

Table R.2.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 27 | 1.3 | 0.65 | 2053 | 38 | 1.9 | 0.90 | 1.38 | (0.84, 2.27) | 0.1972 | |
| Sex | | | | | | | | | | | | 0.3208 |
| Male | 1065 | 16 | 1.5 | 0.74 | 1094 | 19 | 1.7 | 0.85 | 1.10 | (0.56, 2.14) | 0.7824 | |
| Female | 938 | 11 | 1.2 | 0.56 | 959 | 19 | 2.0 | 0.96 | 1.82 | (0.87, 3.84) | 0.1138 | |
| Age [years] | | | | | | | | | | | | 0.9400 |
| <65 | 331 | 4 | 1.2 | 0.58 | 313 | 5 | 1.6 | 0.77 | 1.32 | (0.36, 4.93) | 0.6762 | |
| >=65 | 1672 | 23 | 1.4 | 0.67 | 1740 | 33 | 1.9 | 0.93 | 1.40 | (0.82, 2.38) | 0.2184 | |
| Region | | | | | | | | | | | | 0.2060 |
| North America | 273 | 11 | 4.0 | 1.88 | 274 | 11 | 4.0 | 1.90 | 0.99 | (0.43, 2.28) | 0.9733 | |
| Latin America | 511 | 2 | 0.4 | 0.20 | 504 | 11 | 2.2 | 1.13 | 5.61 | (1.24,25.33) | 0.0248 | |
| Europe | 867 | 8 | 0.9 | 0.44 | 894 | 14 | 1.6 | 0.75 | 1.73 | (0.72, 4.12) | 0.2189 | |
| Asia | 231 | 4 | 1.7 | 0.84 | 248 | 2 | 0.8 | 0.38 | 0.45 | (0.08, 2.43) | 0.3501 | |
| Other | 121 | 2 | 1.7 | 0.83 | 133 | 0 | 0 | 0.00 | <0.01 | | 0.9803 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.0327 |
| Diabetic | 1046 | 23 | 2.2 | 1.08 | 1082 | 23 | 2.1 | 1.04 | 0.97 | (0.55, 1.74) | 0.9265 | |
| Non-Diabetic | 957 | 4 | 0.4 | 0.20 | 971 | 15 | 1.5 | 0.75 | 3.78 | (1.26,11.41) | 0.0181 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1641 |
| <30 | 1087 | 18 | 1.7 | 0.83 | 1094 | 18 | 1.6 | 0.81 | 1.02 | (0.53, 1.97) | 0.9473 | |
| >=30 | 916 | 9 | 1.0 | 0.46 | 959 | 20 | 2.1 | 1.00 | 2.12 | (0.96, 4.65) | 0.0621 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8423 |
| <130 | 827 | 9 | 1.1 | 0.54 | 853 | 15 | 1.8 | 0.86 | 1.50 | (0.65, 3.43) | 0.3419 | |
| >=130 | 1176 | 18 | 1.5 | 0.74 | 1200 | 23 | 1.9 | 0.93 | 1.35 | (0.72, 2.50) | 0.3468 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.0090 |
| <75 | 936 | 10 | 1.1 | 0.52 | 935 | 24 | 2.6 | 1.26 | 2.36 | (1.13, 4.94) | 0.0227 | |
| 75 to <85 | 658 | 17 | 2.6 | 1.26 | 703 | 7 | 1.0 | 0.49 | 0.39 | (0.16, 0.94) | 0.0361 | |
| >=85 | 409 | 0 | 0 | 0.00 | 415 | 7 | 1.7 | 0.81 | >999.99 | | 0.9756 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

Table R.2.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.3308 |
| <30 | 161 | 2 | 1.2 | 0.67 | 148 | 4 | 2.7 | 1.40 | 2.36 | (0.43,12.97) | 0.3250 | |
| 30 to <45 | 550 | 7 | 1.3 | 0.61 | 564 | 15 | 2.7 | 1.31 | 2.12 | (0.87, 5.21) | 0.1001 | |
| >=45 | 1291 | 18 | 1.4 | 0.67 | 1341 | 19 | 1.4 | 0.68 | 1.00 | (0.52, 1.91) | 0.9990 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.5515 |
| Normal (<30) | 766 | 8 | 1.0 | 0.50 | 787 | 14 | 1.8 | 0.85 | 1.81 | (0.76, 4.33) | 0.1790 | |
| Microalbuminuria (30 to <=300) | 921 | 12 | 1.3 | 0.64 | 939 | 13 | 1.4 | 0.67 | 1.00 | (0.46, 2.20) | 0.9996 | |
| Macroalbuminuria (>300) | 311 | 7 | 2.3 | 1.11 | 318 | 11 | 3.5 | 1.78 | 1.69 | (0.65, 4.37) | 0.2810 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4429 |
| Low, moderate or high | 1479 | 19 | 1.3 | 0.62 | 1549 | 24 | 1.5 | 0.74 | 1.21 | (0.66, 2.22) | 0.5295 | |
| Very high | 519 | 8 | 1.5 | 0.77 | 495 | 14 | 2.8 | 1.45 | 1.84 | (0.77, 4.39) | 0.1715 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6361 |
| No | 412 | 6 | 1.5 | 0.72 | 411 | 10 | 2.4 | 1.18 | 1.71 | (0.62, 4.72) | 0.2974 | |
| Yes | 1591 | 21 | 1.3 | 0.64 | 1642 | 28 | 1.7 | 0.83 | 1.29 | (0.73, 2.28) | 0.3714 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.7157 |
| No | 282 | 4 | 1.4 | 0.71 | 277 | 4 | 1.4 | 0.74 | 1.09 | (0.27, 4.36) | 0.9064 | |
| Yes | 1721 | 23 | 1.3 | 0.65 | 1776 | 34 | 1.9 | 0.93 | 1.43 | (0.84, 2.43) | 0.1834 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3551 |
| No | 229 | 5 | 2.2 | 1.04 | 250 | 4 | 1.6 | 0.79 | 0.78 | (0.21, 2.91) | 0.7088 | |
| Yes | 1774 | 22 | 1.2 | 0.60 | 1803 | 34 | 1.9 | 0.92 | 1.52 | (0.89, 2.61) | 0.1244 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

**Figure R.2.1.1.3.2: 1**

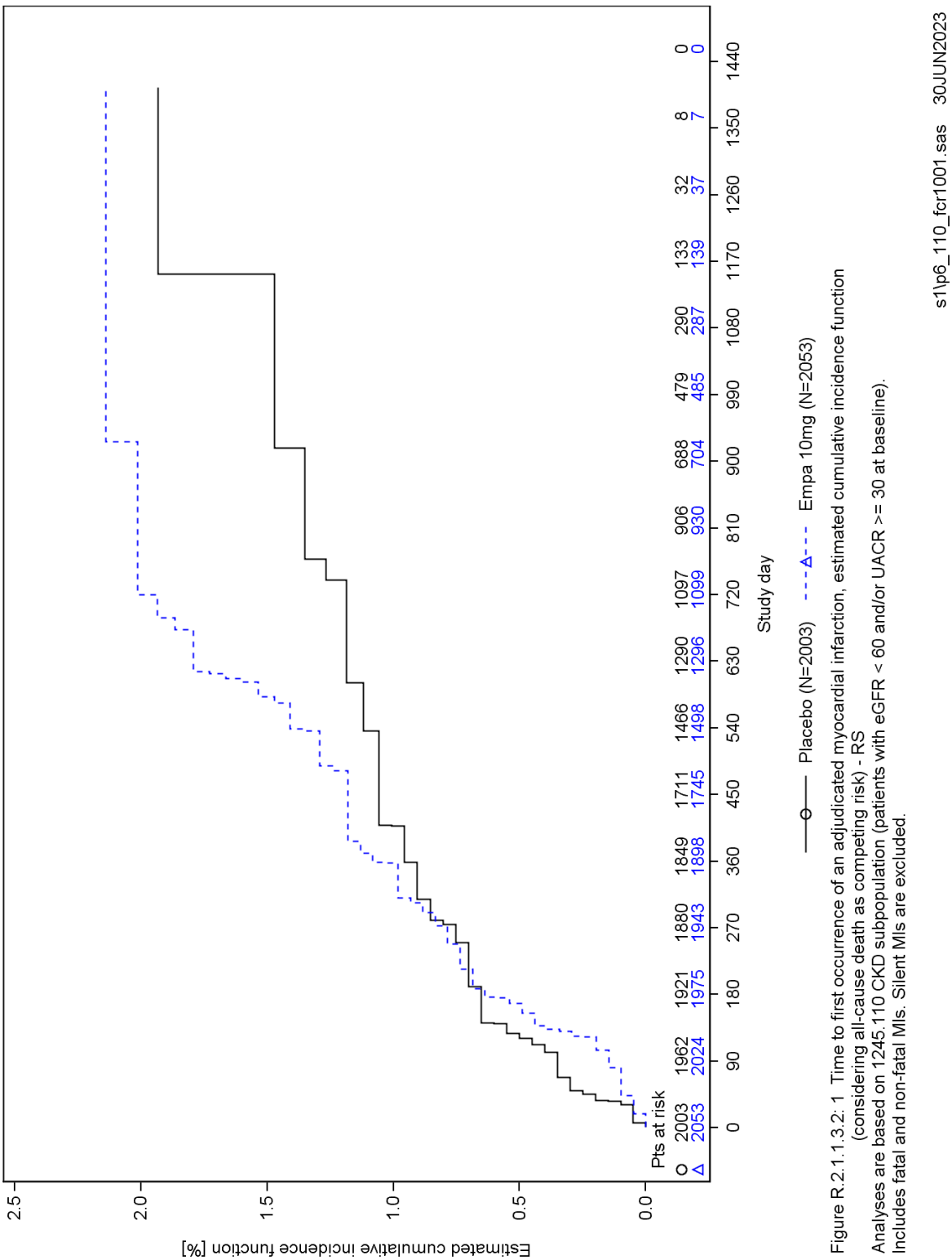


Figure R.2.1.1.3.2: 1 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

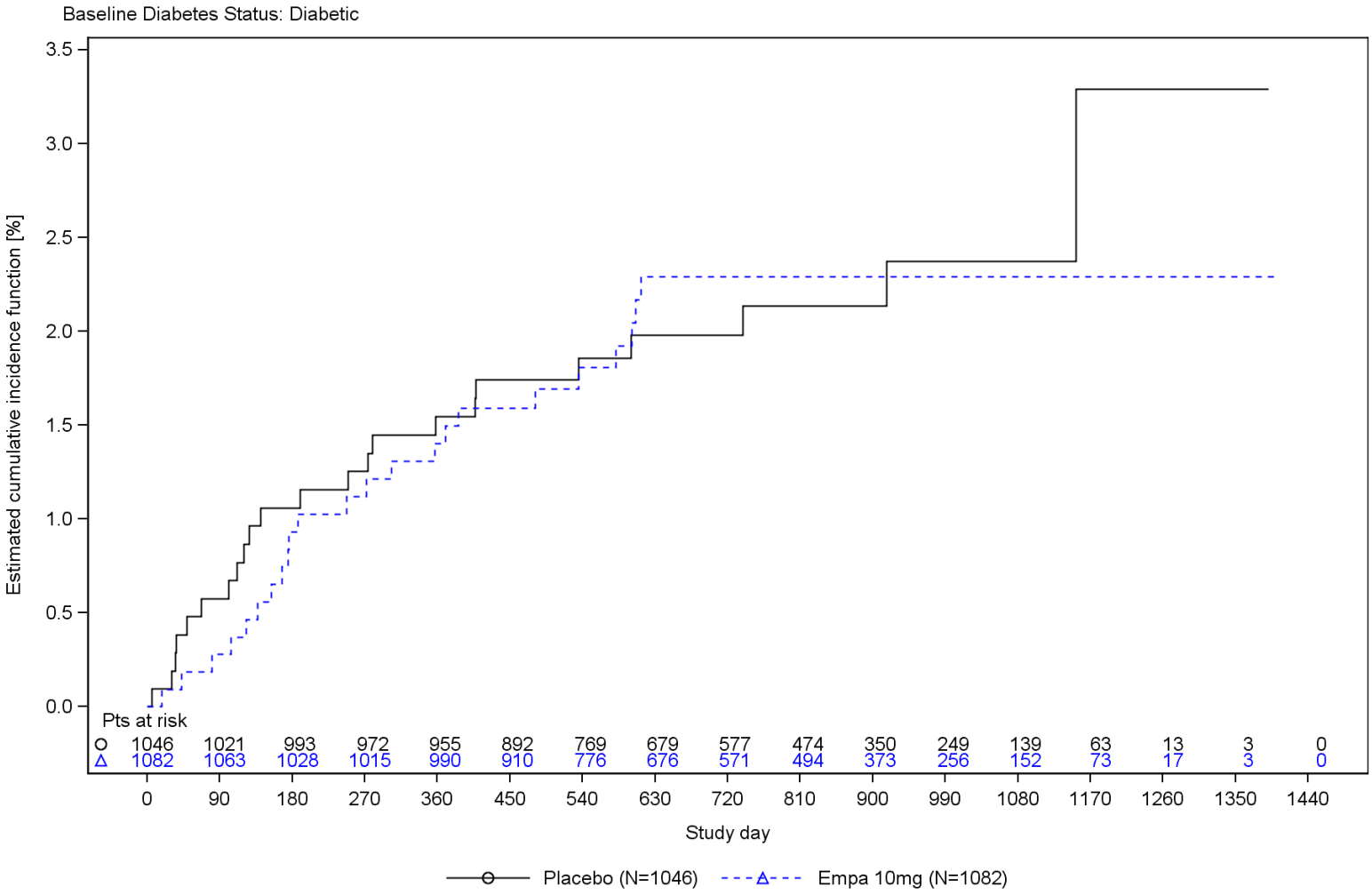


Figure R.2.1.1.3.2: 2 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline diabetes status - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

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**Figure R.2.1.1.3.2: 2**

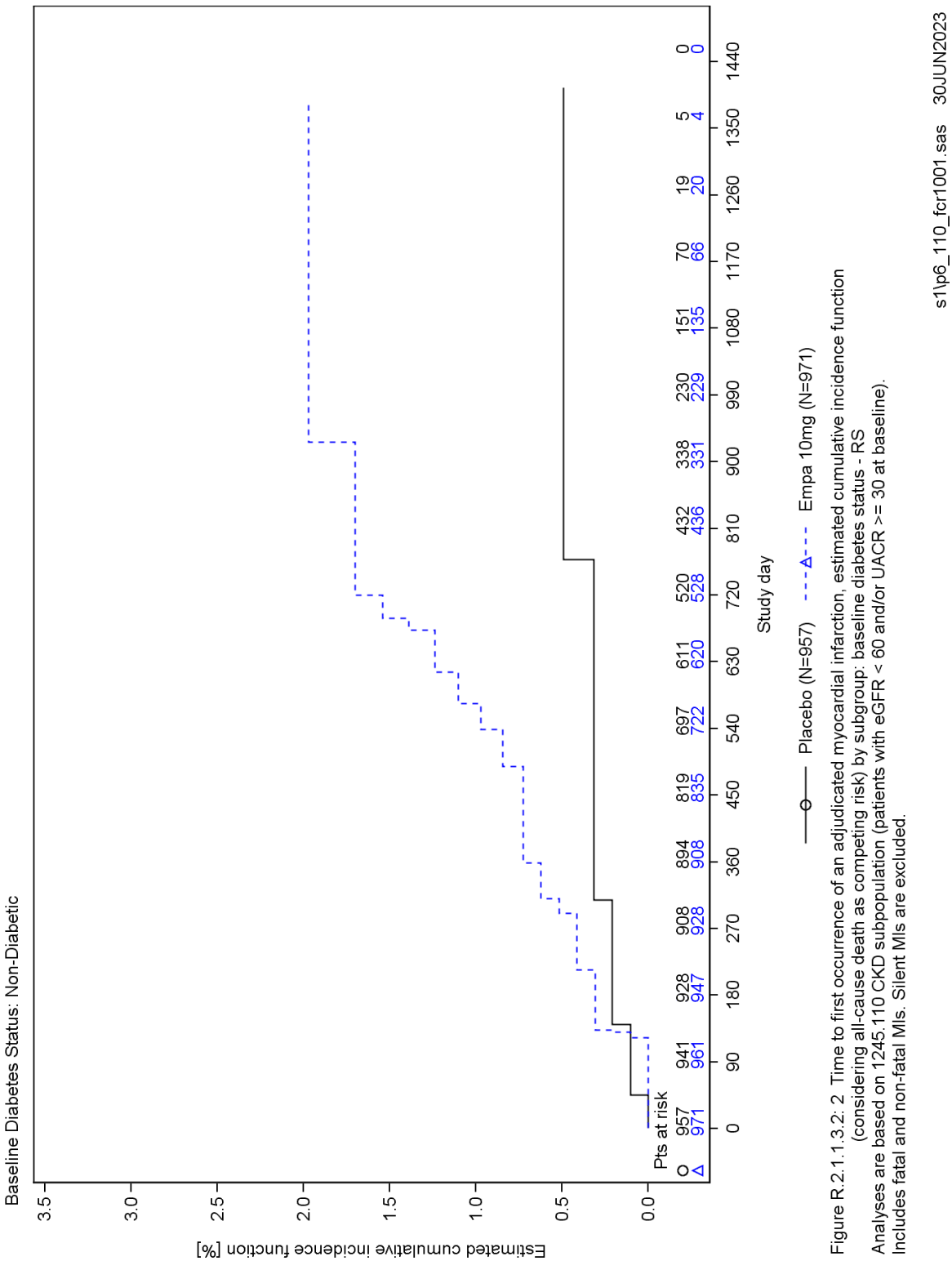


Figure R.2.1.1.3.2: 2 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline diabetes status - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

**Figure R.2.1.1.3.2: 3**

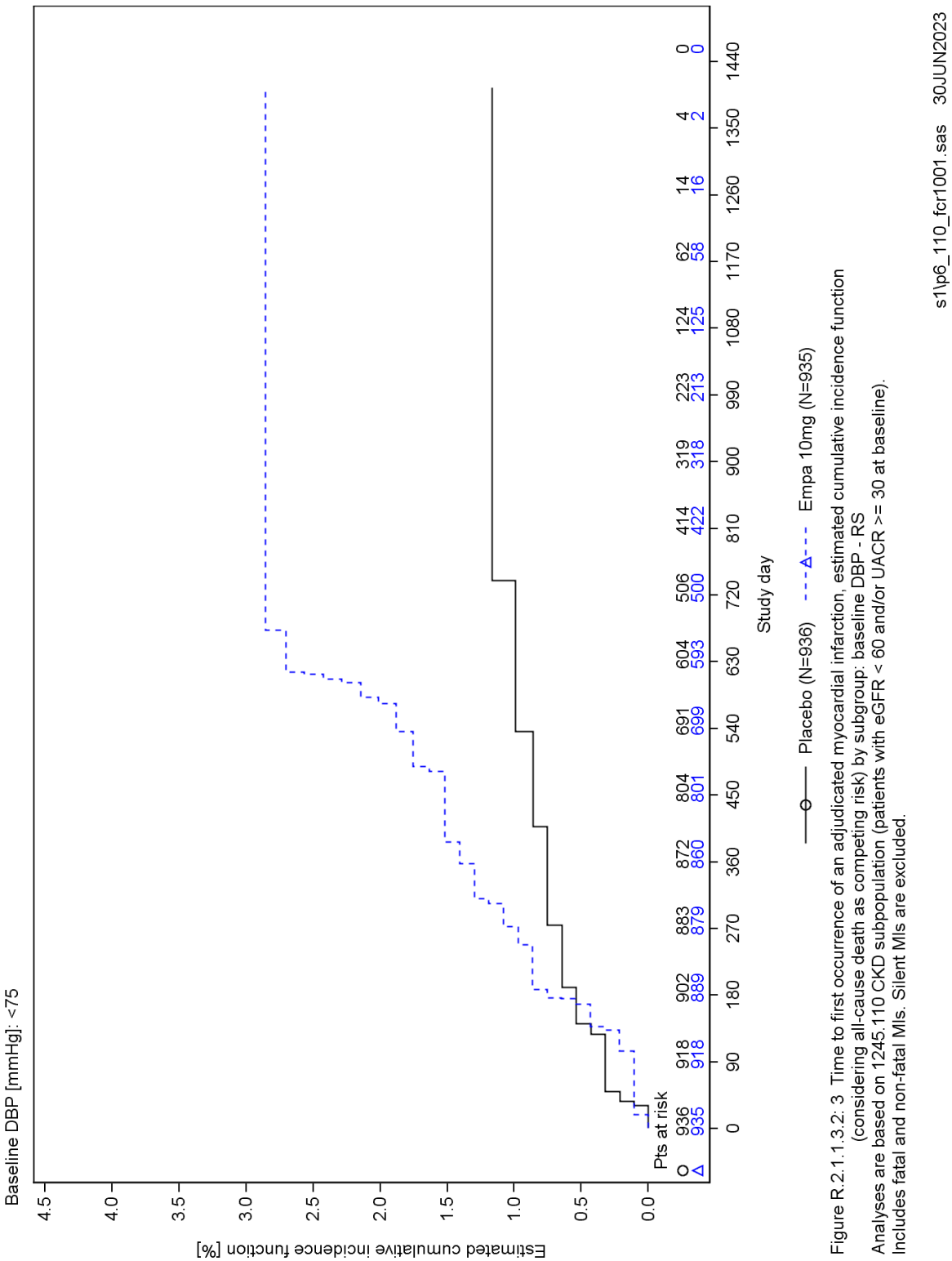


Figure R.2.1.1.3.2: 3 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline DBP - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

**Figure R.2.1.1.3.2: 3**

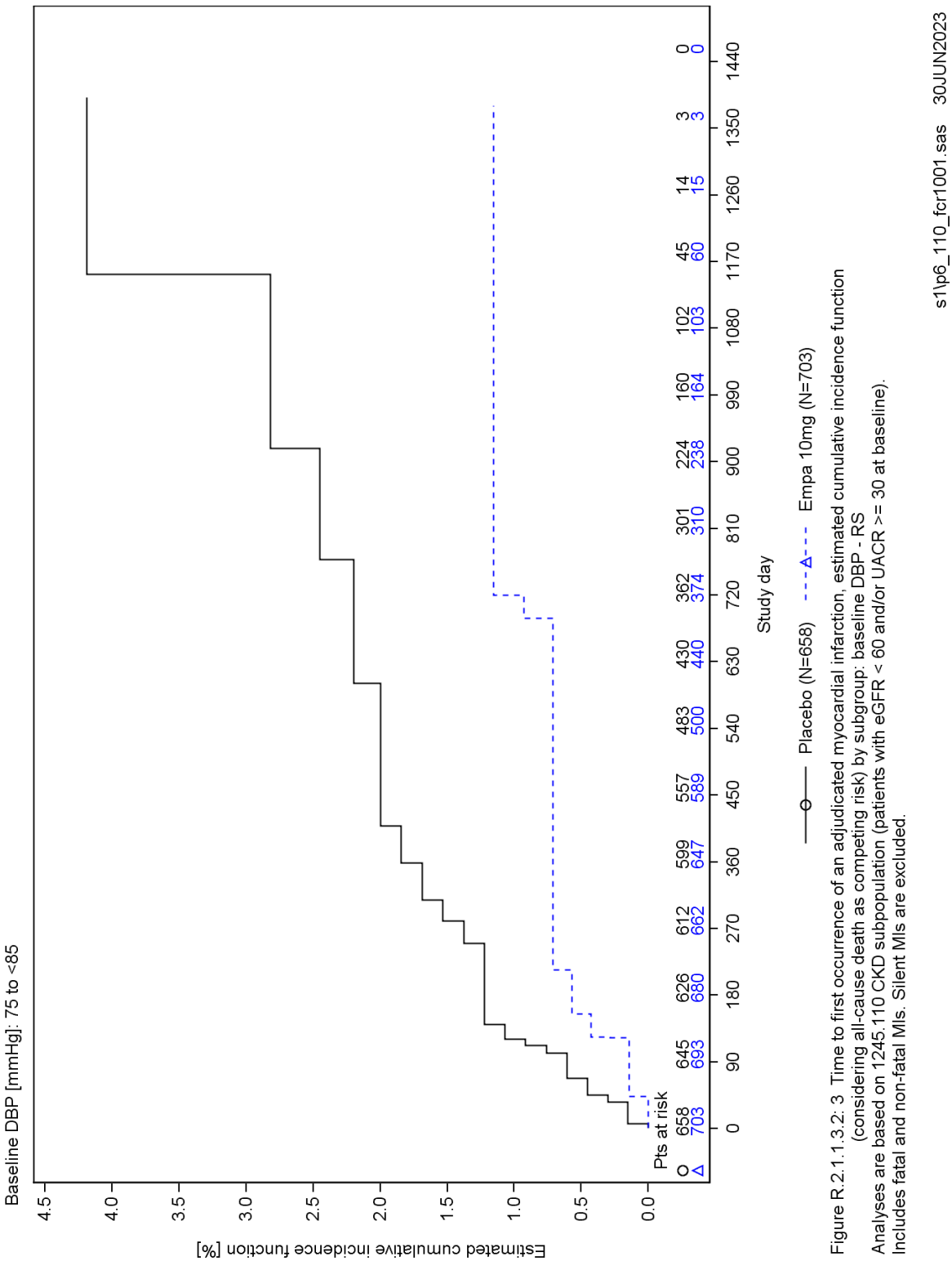


Figure R.2.1.1.3.2: 3 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline DBP - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

**Figure R.2.1.1.3.2: 3**

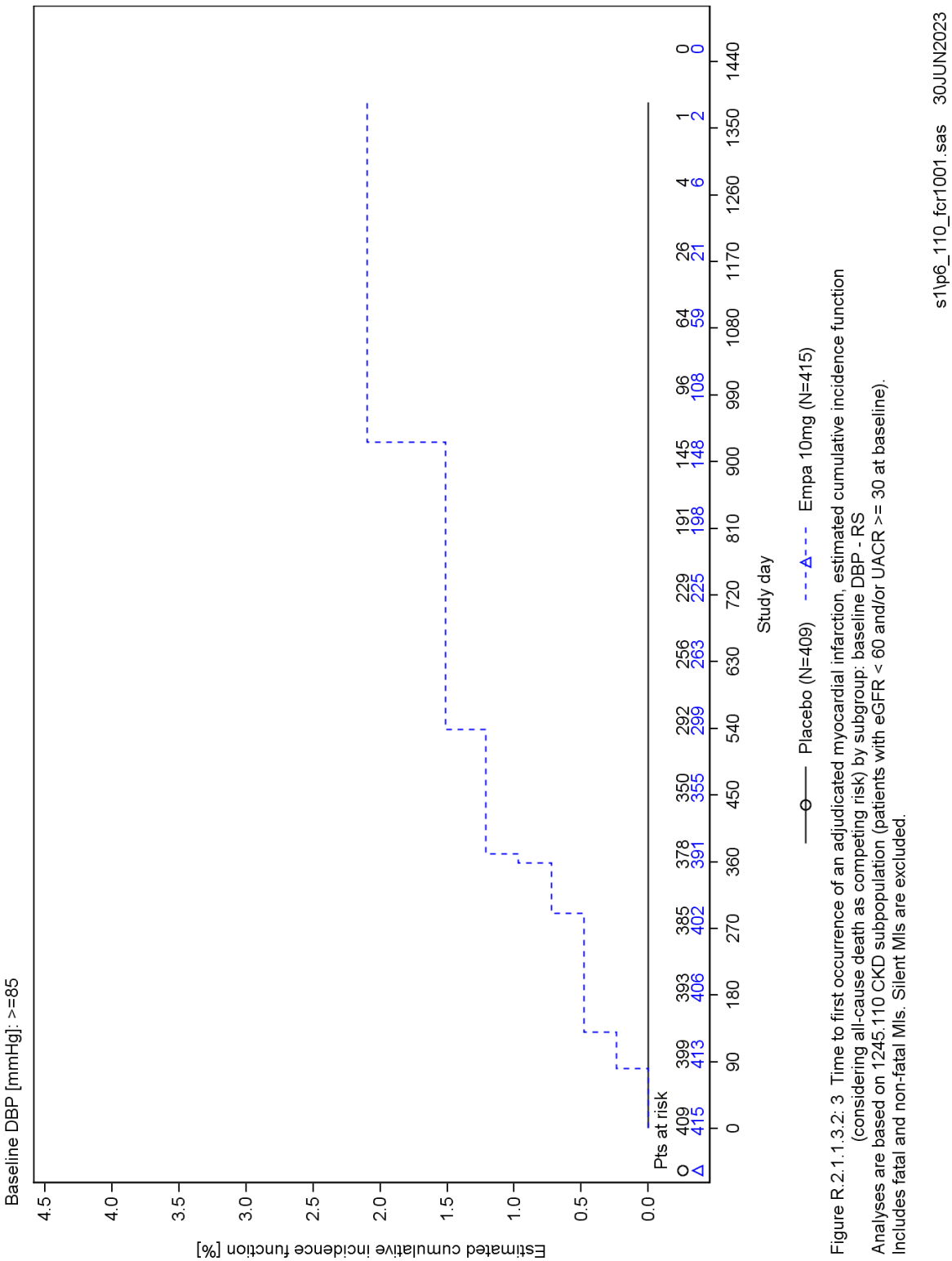


Figure R.2.1.1.3.2: 3 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline DBP - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

R.2.1.1.3.3 Time to first occurrence of an adjudicated stroke

Table R.2.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 67 | 3.3 | 1.63 | 2053 | 70 | 3.4 | 1.67 | 1.02 | (0.73,1.43) | 0.8986 | |
| Sex | | | | | | | | | | | | 0.9816 |
| Male | 1065 | 37 | 3.5 | 1.71 | 1094 | 39 | 3.6 | 1.75 | 1.03 | (0.65,1.61) | 0.9122 | |
| Female | 938 | 30 | 3.2 | 1.55 | 959 | 31 | 3.2 | 1.58 | 1.02 | (0.62,1.68) | 0.9459 | |
| Age [years] | | | | | | | | | | | | 0.0872 |
| <65 | 331 | 12 | 3.6 | 1.75 | 313 | 5 | 1.6 | 0.77 | 0.44 | (0.15,1.24) | 0.1181 | |
| >=65 | 1672 | 55 | 3.3 | 1.61 | 1740 | 65 | 3.7 | 1.83 | 1.14 | (0.80,1.63) | 0.4754 | |
| Region | | | | | | | | | | | | 0.6608 |
| North America | 273 | 14 | 5.1 | 2.40 | 274 | 11 | 4.0 | 1.87 | 0.77 | (0.35,1.70) | 0.5214 | |
| Latin America | 511 | 21 | 4.1 | 2.13 | 504 | 17 | 3.4 | 1.75 | 0.83 | (0.44,1.57) | 0.5594 | |
| Europe | 867 | 19 | 2.2 | 1.05 | 894 | 24 | 2.7 | 1.29 | 1.23 | (0.67,2.25) | 0.4977 | |
| Asia | 231 | 9 | 3.9 | 1.89 | 248 | 15 | 6.0 | 2.88 | 1.53 | (0.67,3.50) | 0.3107 | |
| Other | 121 | 4 | 3.3 | 1.67 | 133 | 3 | 2.3 | 1.18 | 0.72 | (0.16,3.22) | 0.6677 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.6064 |
| Diabetic | 1046 | 36 | 3.4 | 1.68 | 1082 | 35 | 3.2 | 1.58 | 0.94 | (0.59,1.50) | 0.7958 | |
| Non-Diabetic | 957 | 31 | 3.2 | 1.58 | 971 | 35 | 3.6 | 1.77 | 1.12 | (0.69,1.82) | 0.6411 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5219 |
| <30 | 1087 | 41 | 3.8 | 1.90 | 1094 | 39 | 3.6 | 1.77 | 0.93 | (0.60,1.45) | 0.7525 | |
| >=30 | 916 | 26 | 2.8 | 1.34 | 959 | 31 | 3.2 | 1.55 | 1.16 | (0.69,1.96) | 0.5673 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8803 |
| <130 | 827 | 27 | 3.3 | 1.63 | 853 | 29 | 3.4 | 1.68 | 0.99 | (0.59,1.68) | 0.9765 | |
| >=130 | 1176 | 40 | 3.4 | 1.64 | 1200 | 41 | 3.4 | 1.66 | 1.05 | (0.68,1.62) | 0.8412 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6882 |
| <75 | 936 | 37 | 4.0 | 1.94 | 935 | 36 | 3.9 | 1.89 | 0.96 | (0.60,1.51) | 0.8482 | |
| 75 to <85 | 658 | 20 | 3.0 | 1.47 | 703 | 20 | 2.8 | 1.40 | 0.95 | (0.51,1.77) | 0.8797 | |
| >=85 | 409 | 10 | 2.4 | 1.21 | 415 | 14 | 3.4 | 1.63 | 1.42 | (0.63,3.19) | 0.4016 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.2.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6787 |
| <30 | 161 | 3 | 1.9 | 1.01 | 148 | 5 | 3.4 | 1.72 | 1.86 | (0.44,7.83) | 0.3955 | |
| 30 to <45 | 550 | 22 | 4.0 | 1.95 | 564 | 21 | 3.7 | 1.83 | 0.93 | (0.51,1.69) | 0.8045 | |
| >=45 | 1291 | 42 | 3.3 | 1.57 | 1341 | 44 | 3.3 | 1.60 | 1.01 | (0.66,1.54) | 0.9564 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8186 |
| Normal (<30) | 766 | 19 | 2.5 | 1.20 | 787 | 22 | 2.8 | 1.35 | 1.14 | (0.62,2.11) | 0.6729 | |
| Microalbuminuria (30 to <=300) | 921 | 36 | 3.9 | 1.92 | 939 | 34 | 3.6 | 1.77 | 0.92 | (0.58,1.47) | 0.7325 | |
| Macroalbuminuria (>300) | 311 | 12 | 3.9 | 1.92 | 318 | 14 | 4.4 | 2.23 | 1.15 | (0.53,2.49) | 0.7227 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5144 |
| Low, moderate or high | 1479 | 50 | 3.4 | 1.64 | 1549 | 50 | 3.2 | 1.56 | 0.96 | (0.65,1.42) | 0.8295 | |
| Very high | 519 | 17 | 3.3 | 1.64 | 495 | 20 | 4.0 | 2.05 | 1.23 | (0.64,2.36) | 0.5273 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.1912 |
| No | 412 | 9 | 2.2 | 1.08 | 411 | 15 | 3.6 | 1.78 | 1.68 | (0.74,3.85) | 0.2180 | |
| Yes | 1591 | 58 | 3.6 | 1.78 | 1642 | 55 | 3.3 | 1.64 | 0.92 | (0.64,1.33) | 0.6543 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.7011 |
| No | 282 | 9 | 3.2 | 1.60 | 277 | 7 | 2.5 | 1.29 | 0.85 | (0.32,2.28) | 0.7467 | |
| Yes | 1721 | 58 | 3.4 | 1.64 | 1776 | 63 | 3.5 | 1.73 | 1.04 | (0.73,1.49) | 0.8135 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.0601 |
| No | 229 | 17 | 7.4 | 3.58 | 250 | 9 | 3.6 | 1.79 | 0.51 | (0.23,1.14) | 0.1018 | |
| Yes | 1774 | 50 | 2.8 | 1.38 | 1803 | 61 | 3.4 | 1.65 | 1.20 | (0.82,1.74) | 0.3449 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.3: 1**

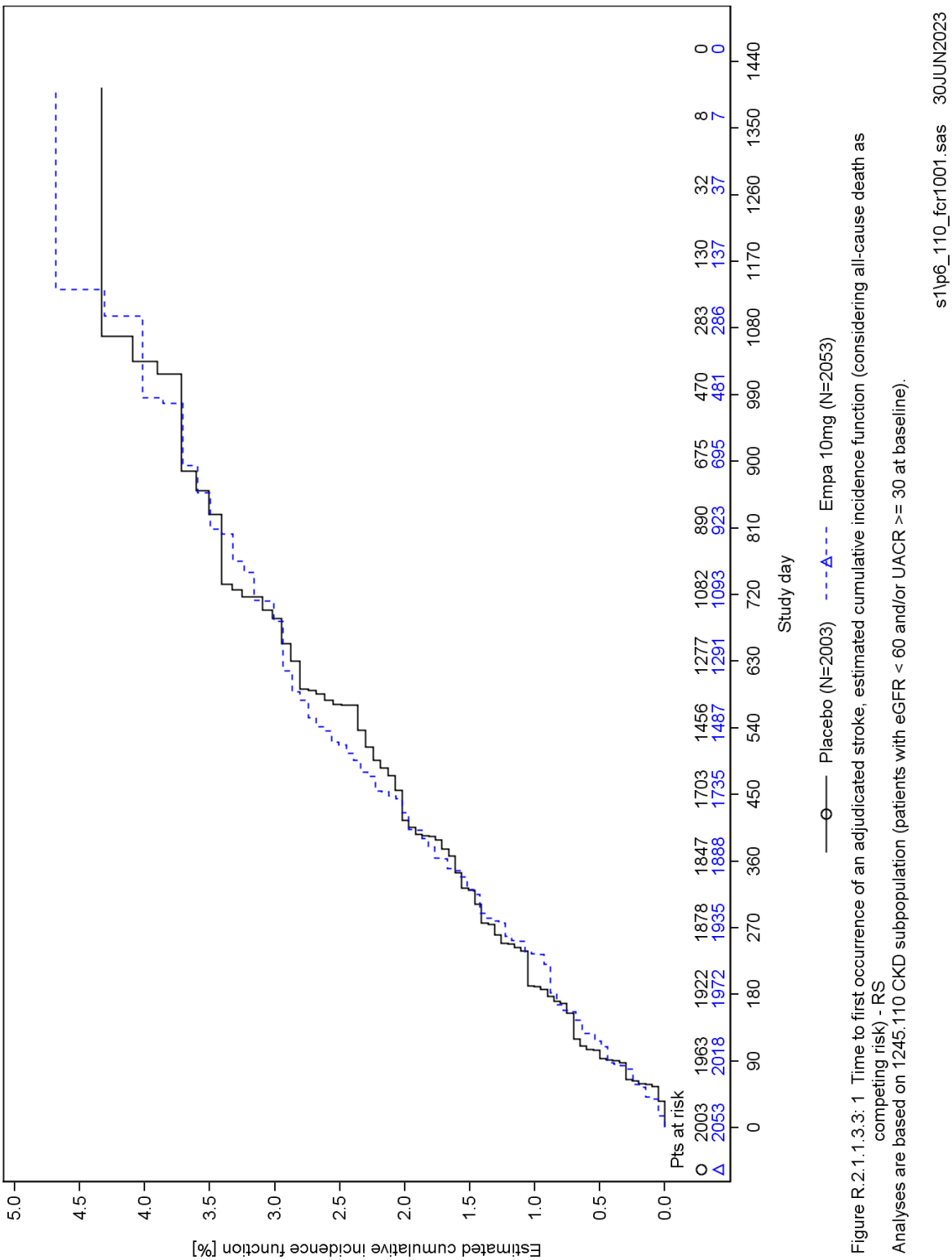


Figure R.2.1.1.3.3: 1 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.2.1.1.3.4 Time to first adjudicated hospitalization for heart failure

Table R.2.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 294 | 14.7 | 7.70 | 2053 | 223 | 10.9 | 5.52 | 0.71 | (0.60,0.85) | 0.0001 | |
| Sex | | | | | | | | | | | | 0.5648 |
| Male | 1065 | 163 | 15.3 | 8.17 | 1094 | 133 | 12.2 | 6.25 | 0.74 | (0.59,0.93) | 0.0109 | |
| Female | 938 | 131 | 14.0 | 7.18 | 959 | 90 | 9.4 | 4.71 | 0.67 | (0.51,0.88) | 0.0034 | |
| Age [years] | | | | | | | | | | | | 0.1621 |
| <65 | 331 | 43 | 13.0 | 6.69 | 313 | 40 | 12.8 | 6.56 | 0.94 | (0.61,1.45) | 0.7854 | |
| >=65 | 1672 | 251 | 15.0 | 7.90 | 1740 | 183 | 10.5 | 5.34 | 0.67 | (0.56,0.81) | <0.0001 | |
| Region | | | | | | | | | | | | 0.3203 |
| North America | 273 | 58 | 21.2 | 11.10 | 274 | 47 | 17.2 | 8.62 | 0.77 | (0.53,1.14) | 0.1886 | |
| Latin America | 511 | 50 | 9.8 | 5.26 | 504 | 45 | 8.9 | 4.74 | 0.90 | (0.60,1.35) | 0.6067 | |
| Europe | 867 | 120 | 13.8 | 7.09 | 894 | 77 | 8.6 | 4.26 | 0.60 | (0.45,0.79) | 0.0004 | |
| Asia | 231 | 46 | 19.9 | 10.67 | 248 | 33 | 13.3 | 6.68 | 0.61 | (0.39,0.96) | 0.0308 | |
| Other | 121 | 20 | 16.5 | 8.97 | 133 | 21 | 15.8 | 8.77 | 1.01 | (0.55,1.87) | 0.9623 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.4103 |
| Diabetic | 1046 | 186 | 17.8 | 9.56 | 1082 | 136 | 12.6 | 6.52 | 0.67 | (0.54,0.84) | 0.0004 | |
| Non-Diabetic | 957 | 108 | 11.3 | 5.77 | 971 | 87 | 9.0 | 4.46 | 0.78 | (0.59,1.04) | 0.0871 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.6811 |
| <30 | 1087 | 162 | 14.9 | 8.03 | 1094 | 117 | 10.7 | 5.49 | 0.69 | (0.54,0.87) | 0.0020 | |
| >=30 | 916 | 132 | 14.4 | 7.33 | 959 | 106 | 11.1 | 5.56 | 0.74 | (0.57,0.96) | 0.0208 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8118 |
| <130 | 827 | 128 | 15.5 | 8.37 | 853 | 99 | 11.6 | 5.93 | 0.69 | (0.53,0.90) | 0.0062 | |
| >=130 | 1176 | 166 | 14.1 | 7.25 | 1200 | 124 | 10.3 | 5.24 | 0.72 | (0.57,0.91) | 0.0063 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.8797 |
| <75 | 936 | 150 | 16.0 | 8.47 | 935 | 116 | 12.4 | 6.33 | 0.73 | (0.58,0.94) | 0.0124 | |
| 75 to <85 | 658 | 94 | 14.3 | 7.38 | 703 | 67 | 9.5 | 4.87 | 0.66 | (0.49,0.91) | 0.0107 | |
| >=85 | 409 | 50 | 12.2 | 6.45 | 415 | 40 | 9.6 | 4.83 | 0.73 | (0.48,1.11) | 0.1376 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.2.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8100 |
| <30 | 161 | 43 | 26.7 | 16.64 | 148 | 36 | 24.3 | 13.90 | 0.80 | (0.51,1.25) | 0.3278 | |
| 30 to <45 | 550 | 99 | 18.0 | 9.62 | 564 | 70 | 12.4 | 6.38 | 0.67 | (0.49,0.91) | 0.0102 | |
| >=45 | 1291 | 152 | 11.8 | 6.01 | 1341 | 117 | 8.7 | 4.37 | 0.72 | (0.56,0.91) | 0.0066 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9128 |
| Normal (<30) | 766 | 84 | 11.0 | 5.57 | 787 | 60 | 7.6 | 3.74 | 0.70 | (0.50,0.97) | 0.0334 | |
| Microalbuminuria (30 to <=300) | 921 | 137 | 14.9 | 7.85 | 939 | 104 | 11.1 | 5.65 | 0.70 | (0.54,0.90) | 0.0053 | |
| Macroalbuminuria (>300) | 311 | 72 | 23.2 | 12.99 | 318 | 59 | 18.6 | 10.30 | 0.76 | (0.54,1.07) | 0.1192 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5071 |
| Low, moderate or high | 1479 | 169 | 11.4 | 5.83 | 1549 | 136 | 8.8 | 4.37 | 0.75 | (0.60,0.94) | 0.0138 | |
| Very high | 519 | 124 | 23.9 | 13.61 | 495 | 87 | 17.6 | 9.64 | 0.67 | (0.51,0.88) | 0.0040 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7675 |
| No | 412 | 80 | 19.4 | 10.48 | 411 | 60 | 14.6 | 7.56 | 0.74 | (0.53,1.04) | 0.0849 | |
| Yes | 1591 | 214 | 13.5 | 7.00 | 1642 | 163 | 9.9 | 5.03 | 0.70 | (0.57,0.86) | 0.0007 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5914 |
| No | 282 | 40 | 14.2 | 7.59 | 277 | 31 | 11.2 | 5.97 | 0.80 | (0.50,1.28) | 0.3544 | |
| Yes | 1721 | 254 | 14.8 | 7.71 | 1776 | 192 | 10.8 | 5.46 | 0.70 | (0.58,0.84) | 0.0002 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.5103 |
| No | 229 | 13 | 5.7 | 2.74 | 250 | 7 | 2.8 | 1.38 | 0.52 | (0.21,1.31) | 0.1664 | |
| Yes | 1774 | 281 | 15.8 | 8.40 | 1803 | 216 | 12.0 | 6.12 | 0.72 | (0.60,0.85) | 0.0002 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.4: 1**

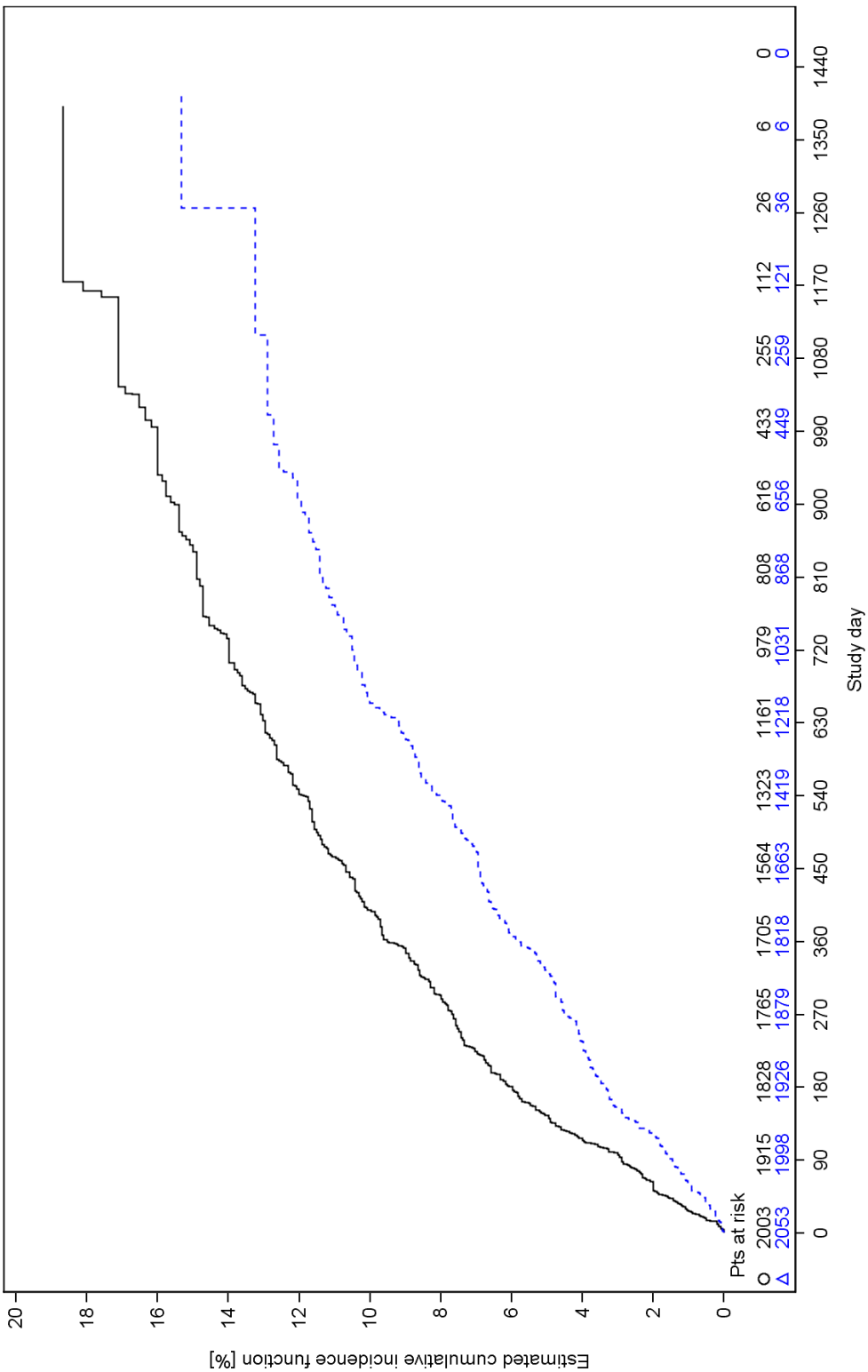


Figure R.2.1.1.3.4: 1 Time to first occurrence of an adjudicated HHF, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.2.1.1.3.5 Time to occurrence of adjudicated hospitalization for heart failure (first and recurrent)

Table R.2.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 294 | 14.7 | 456 | 10.96 | 2053 | 223 | 10.9 | 346 | 8.13 | 0.70 | (0.57,0.86) | 0.0008 | |
| Sex | | | | | | | | | | | | | | 0.4139 |
| Male | 1065 | 163 | 15.3 | 258 | 11.75 | 1094 | 133 | 12.2 | 225 | 9.94 | 0.76 | (0.58,1.00) | 0.0462 | |
| Female | 938 | 131 | 14.0 | 198 | 10.07 | 959 | 90 | 9.4 | 121 | 6.07 | 0.64 | (0.47,0.87) | 0.0048 | |
| Age [years] | | | | | | | | | | | | | | 0.0201 |
| <65 | 331 | 43 | 13.0 | 64 | 9.18 | 313 | 40 | 12.8 | 65 | 9.94 | 1.22 | (0.73,2.04) | 0.4442 | |
| >=65 | 1672 | 251 | 15.0 | 392 | 11.32 | 1740 | 183 | 10.5 | 281 | 7.80 | 0.63 | (0.50,0.79) | <0.0001 | |
| Region | | | | | | | | | | | | | | 0.0184 |
| North America | 273 | 58 | 21.2 | 79 | 13.20 | 274 | 47 | 17.2 | 87 | 14.63 | 1.26 | (0.77,2.06) | 0.3591 | |
| Latin America | 511 | 50 | 9.8 | 71 | 7.07 | 504 | 45 | 8.9 | 64 | 6.49 | 0.89 | (0.56,1.39) | 0.5954 | |
| Europe | 867 | 120 | 13.8 | 184 | 10.05 | 894 | 77 | 8.6 | 104 | 5.52 | 0.52 | (0.38,0.72) | <0.0001 | |
| Asia | 231 | 46 | 19.9 | 91 | 18.79 | 248 | 33 | 13.3 | 56 | 10.51 | 0.50 | (0.29,0.85) | 0.0111 | |
| Other | 121 | 20 | 16.5 | 31 | 12.72 | 133 | 21 | 15.8 | 35 | 13.56 | 0.96 | (0.45,2.04) | 0.9125 | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7463 |
| Diabetic | 1046 | 186 | 17.8 | 291 | 13.39 | 1082 | 136 | 12.6 | 222 | 9.93 | 0.69 | (0.52,0.90) | 0.0072 | |
| Non-Diabetic | 957 | 108 | 11.3 | 165 | 8.30 | 971 | 87 | 9.0 | 124 | 6.14 | 0.74 | (0.54,1.01) | 0.0596 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1283 |
| <30 | 1087 | 162 | 14.9 | 265 | 12.08 | 1094 | 117 | 10.7 | 179 | 8.00 | 0.61 | (0.46,0.80) | 0.0005 | |
| >=30 | 916 | 132 | 14.4 | 191 | 9.71 | 959 | 106 | 11.1 | 167 | 8.27 | 0.84 | (0.62,1.13) | 0.2444 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7532 |
| <130 | 827 | 128 | 15.5 | 216 | 12.81 | 853 | 99 | 11.6 | 169 | 9.60 | 0.73 | (0.53,0.99) | 0.0407 | |
| >=130 | 1176 | 166 | 14.1 | 240 | 9.70 | 1200 | 124 | 10.3 | 177 | 7.09 | 0.68 | (0.52,0.89) | 0.0060 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2776 |
| <75 | 936 | 150 | 16.0 | 244 | 12.55 | 935 | 116 | 12.4 | 193 | 9.96 | 0.76 | (0.57,1.02) | 0.0655 | |
| 75 to <85 | 658 | 94 | 14.3 | 140 | 10.17 | 703 | 67 | 9.5 | 90 | 6.23 | 0.55 | (0.38,0.80) | 0.0016 | |
| >=85 | 409 | 50 | 12.2 | 72 | 8.57 | 415 | 40 | 9.6 | 63 | 7.21 | 0.85 | (0.53,1.36) | 0.4931 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline LVEF, baseline diabetes status, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.2.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7045 |
| <30 | 161 | 43 | 26.7 | 72 | 23.94 | 148 | 36 | 24.3 | 51 | 17.39 | 0.66 | (0.35,1.24) | 0.1971 | |
| 30 to <45 | 550 | 99 | 18.0 | 134 | 11.67 | 564 | 70 | 12.4 | 112 | 9.59 | 0.82 | (0.56,1.19) | 0.2863 | |
| >=45 | 1291 | 152 | 11.8 | 250 | 9.22 | 1341 | 117 | 8.7 | 183 | 6.55 | 0.68 | (0.52,0.88) | 0.0040 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6021 |
| Normal (<30) | 766 | 84 | 11.0 | 132 | 8.21 | 787 | 60 | 7.6 | 85 | 5.14 | 0.63 | (0.44,0.91) | 0.0124 | |
| Microalbuminuria (30 to <=300) | 921 | 137 | 14.9 | 202 | 10.61 | 939 | 104 | 11.1 | 174 | 8.93 | 0.79 | (0.59,1.07) | 0.1303 | |
| Macroalbuminuria (>300) | 311 | 72 | 23.2 | 121 | 18.97 | 318 | 59 | 18.6 | 87 | 13.72 | 0.67 | (0.42,1.06) | 0.0834 | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9590 |
| Low, moderate or high | 1479 | 169 | 11.4 | 263 | 8.47 | 1549 | 136 | 8.8 | 202 | 6.22 | 0.73 | (0.57,0.93) | 0.0128 | |
| Very high | 519 | 124 | 23.9 | 192 | 18.35 | 495 | 87 | 17.6 | 144 | 14.59 | 0.74 | (0.51,1.06) | 0.0981 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6697 |
| No | 412 | 80 | 19.4 | 129 | 15.26 | 411 | 60 | 14.6 | 106 | 12.33 | 0.76 | (0.50,1.15) | 0.1964 | |
| Yes | 1591 | 214 | 13.5 | 327 | 9.86 | 1642 | 163 | 9.9 | 240 | 7.07 | 0.68 | (0.54,0.87) | 0.0017 | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6887 |
| No | 282 | 40 | 14.2 | 63 | 11.10 | 277 | 31 | 11.2 | 50 | 9.16 | 0.78 | (0.45,1.36) | 0.3788 | |
| Yes | 1721 | 254 | 14.8 | 393 | 10.94 | 1776 | 192 | 10.8 | 296 | 7.98 | 0.69 | (0.55,0.86) | 0.0011 | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3726 |
| No | 229 | 13 | 5.7 | 18 | 3.69 | 250 | 7 | 2.8 | 9 | 1.76 | 0.47 | (0.19,1.17) | 0.1026 | |
| Yes | 1774 | 281 | 15.8 | 438 | 11.92 | 1803 | 216 | 12.0 | 337 | 9.00 | 0.72 | (0.58,0.88) | 0.0019 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline LVEF, baseline diabetes status, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.5: 1**

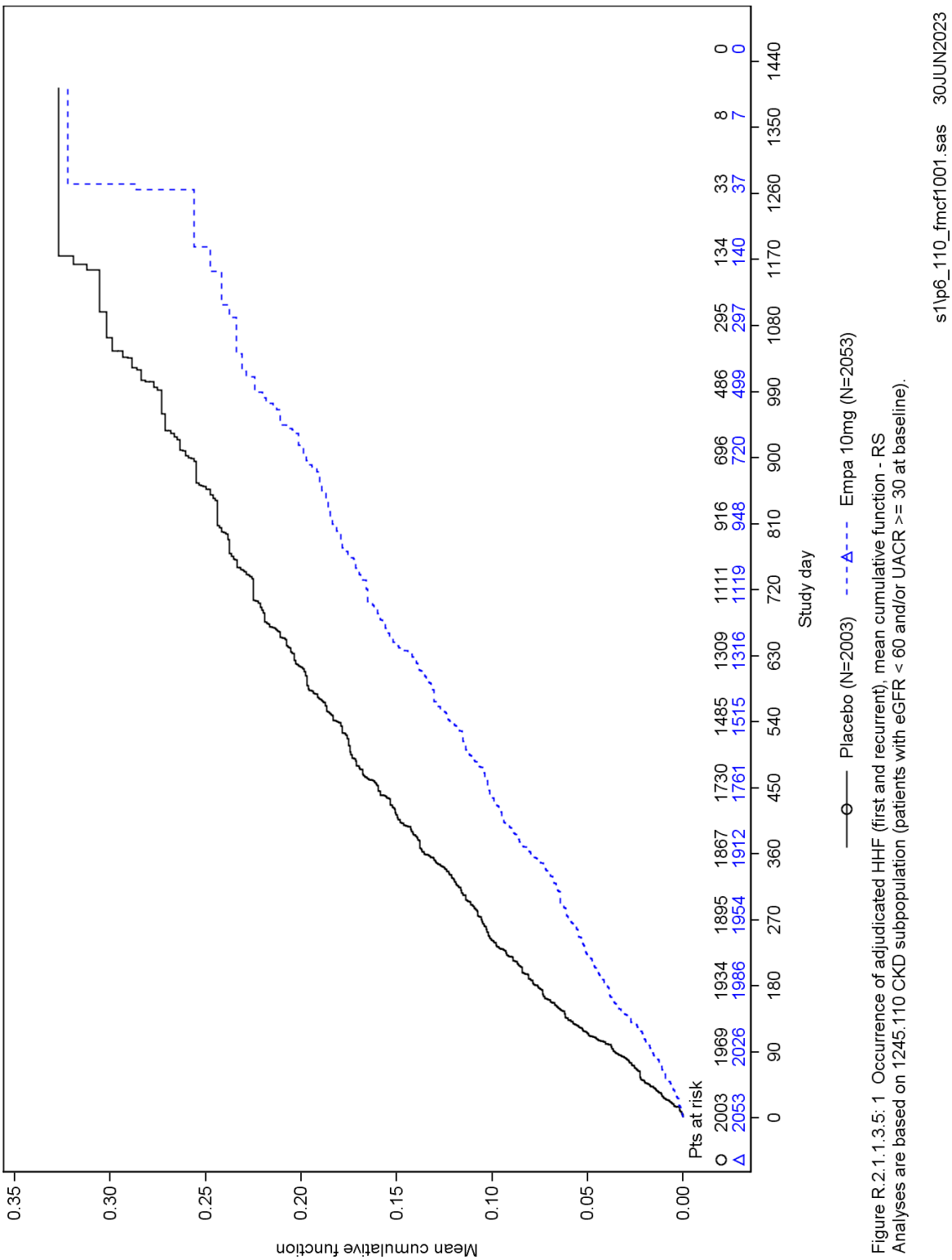


Figure R.2.1.1.3.5: 1 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.5: 2**

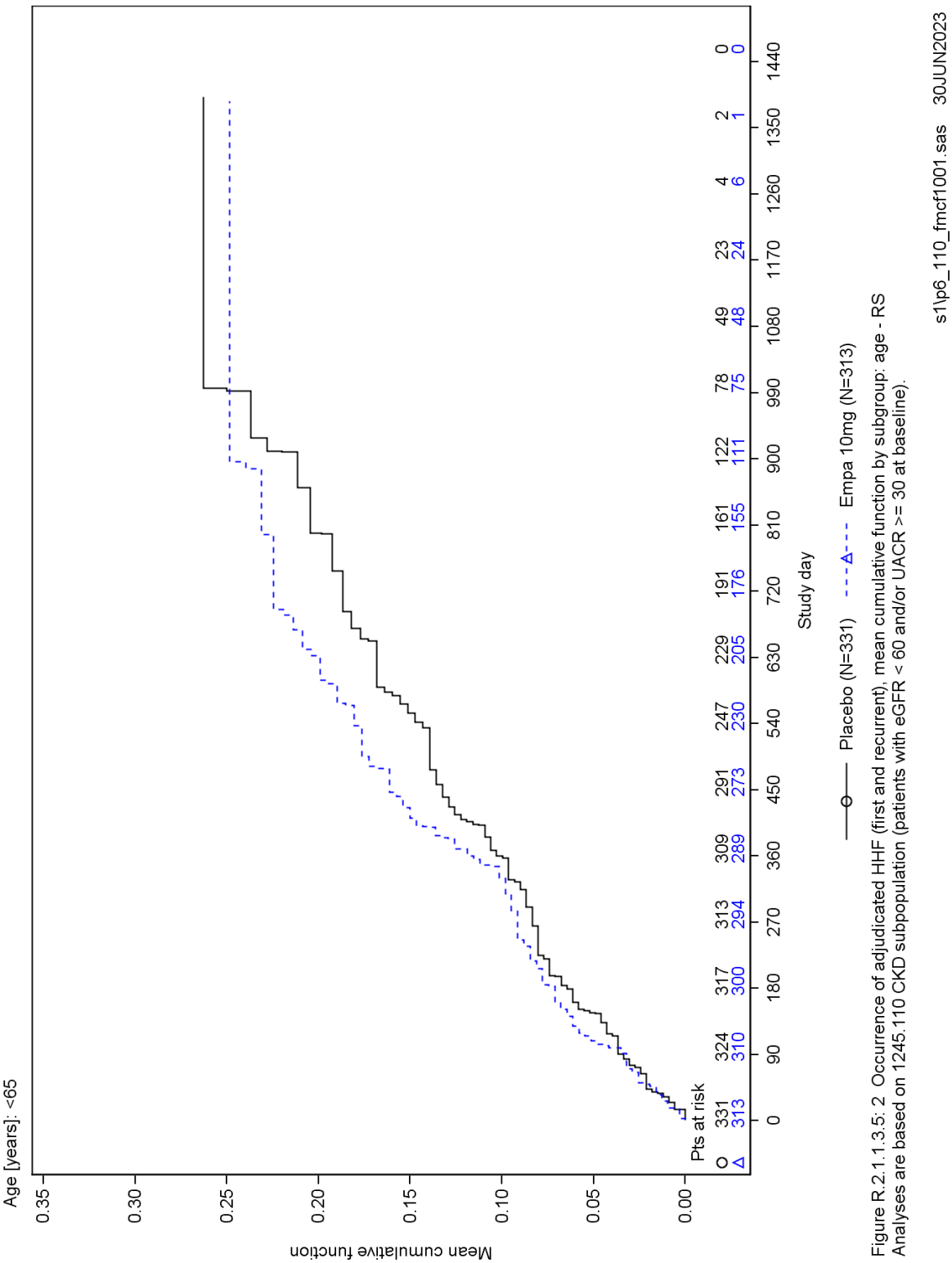


Figure R.2.1.1.3.5: 2 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: age - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.5: 2**

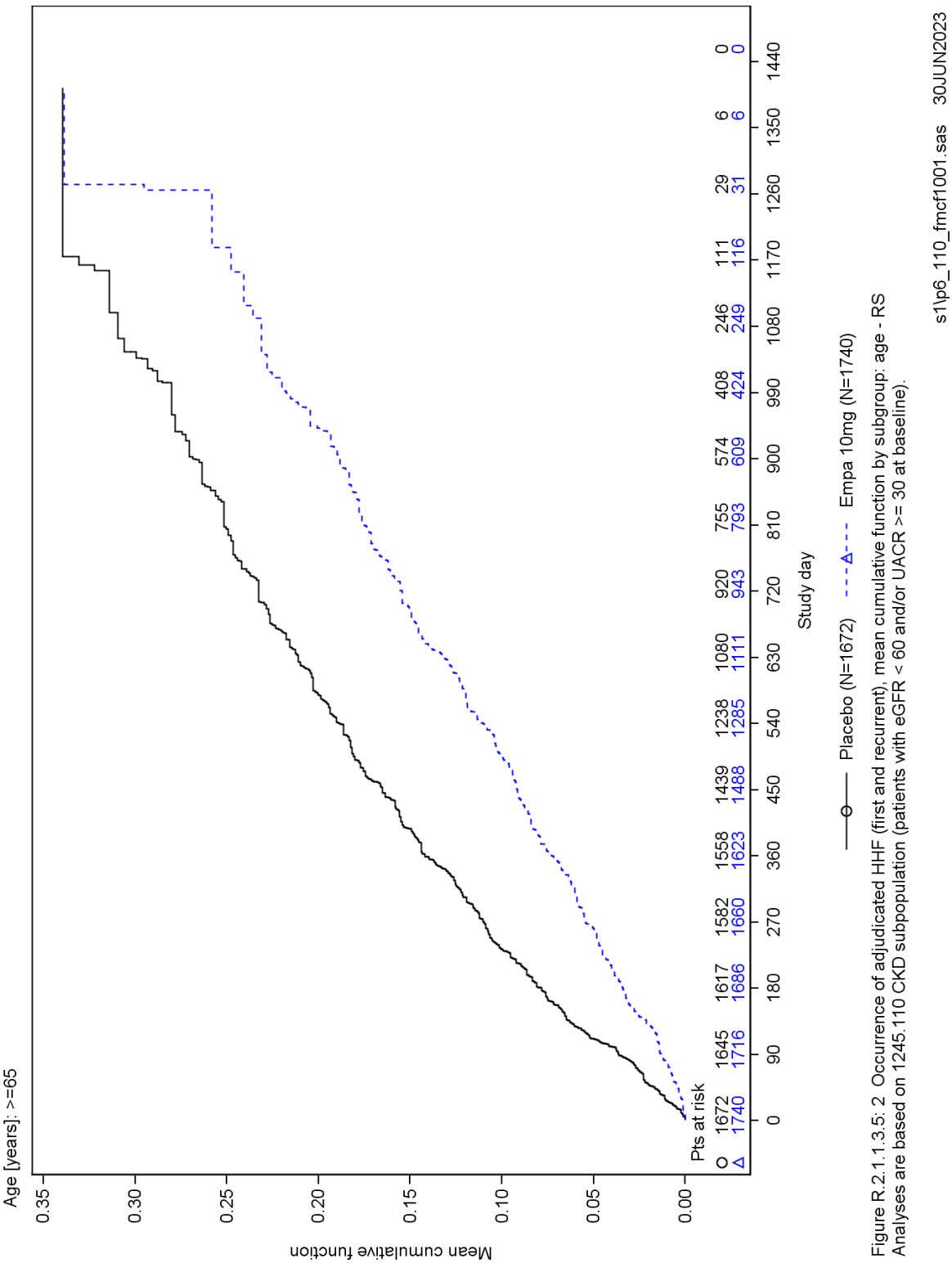


Figure R.2.1.1.3.5: 2 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: age - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.5: 3**

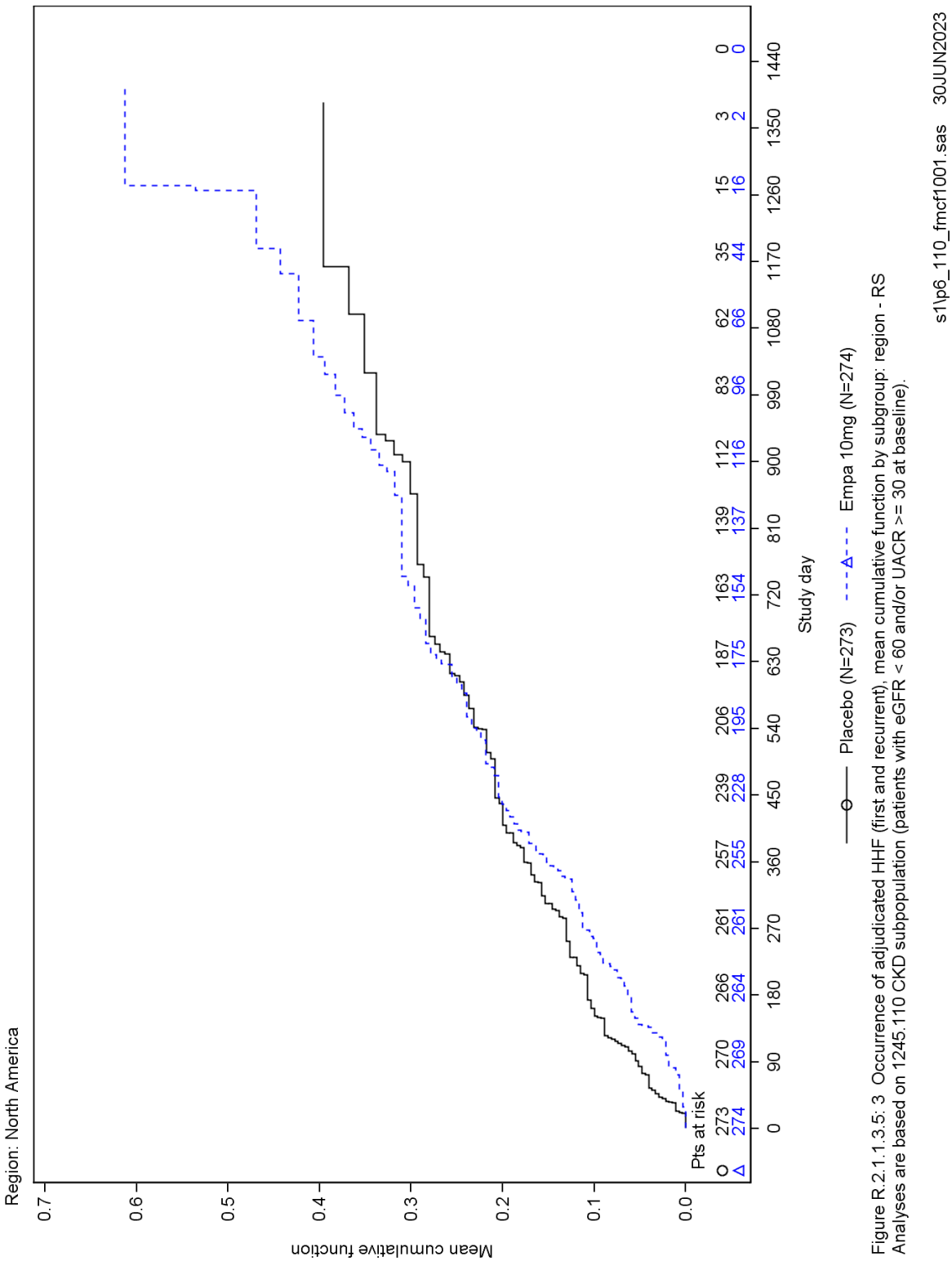


Figure R.2.1.1.3.5: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: region - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.5: 3**

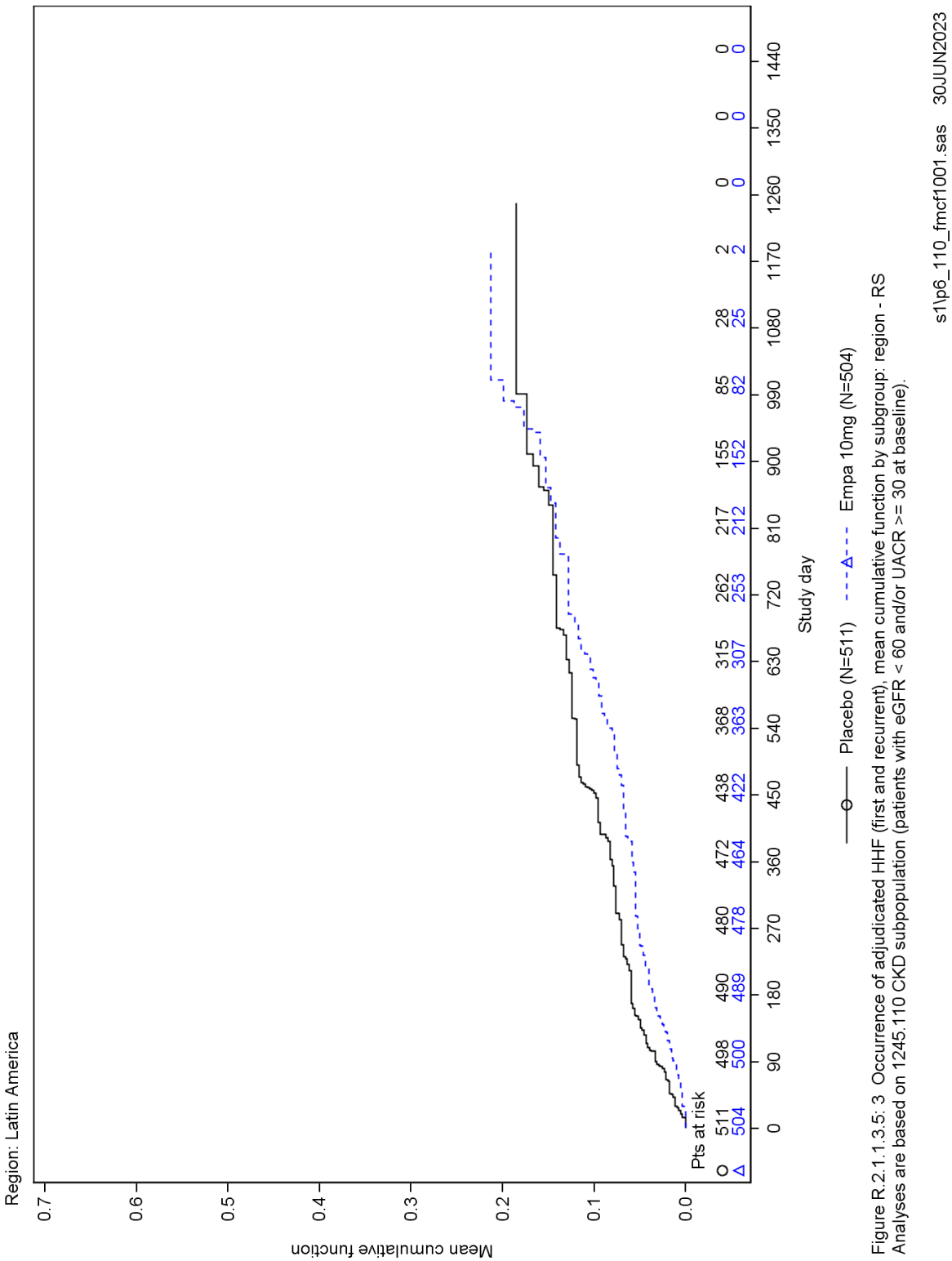


Figure R.2.1.1.3.5: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: region - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.5: 3**

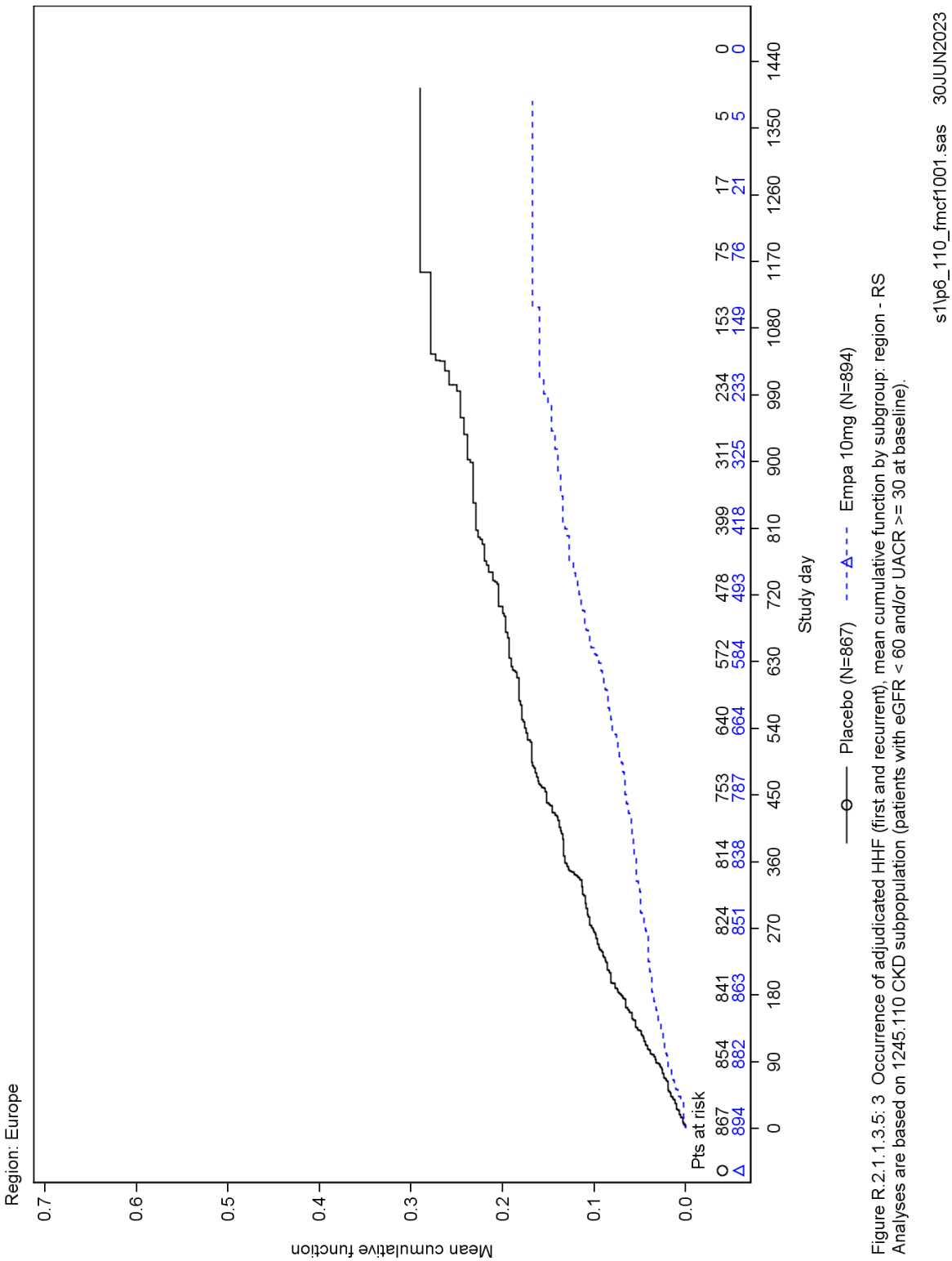


Figure R.2.1.1.3.5: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: region - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.5: 3**

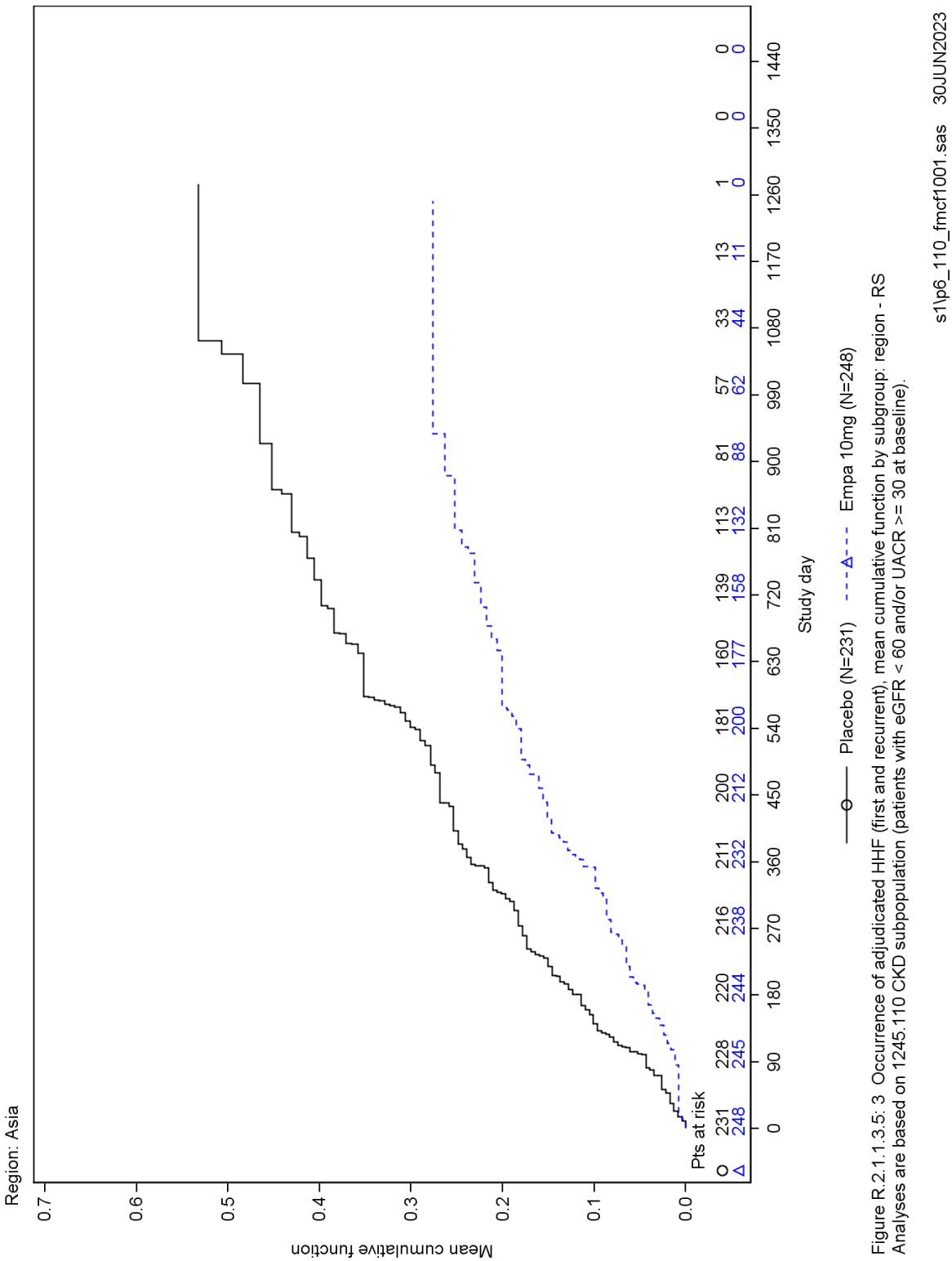


Figure R.2.1.1.3.5: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: region - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.5: 3**

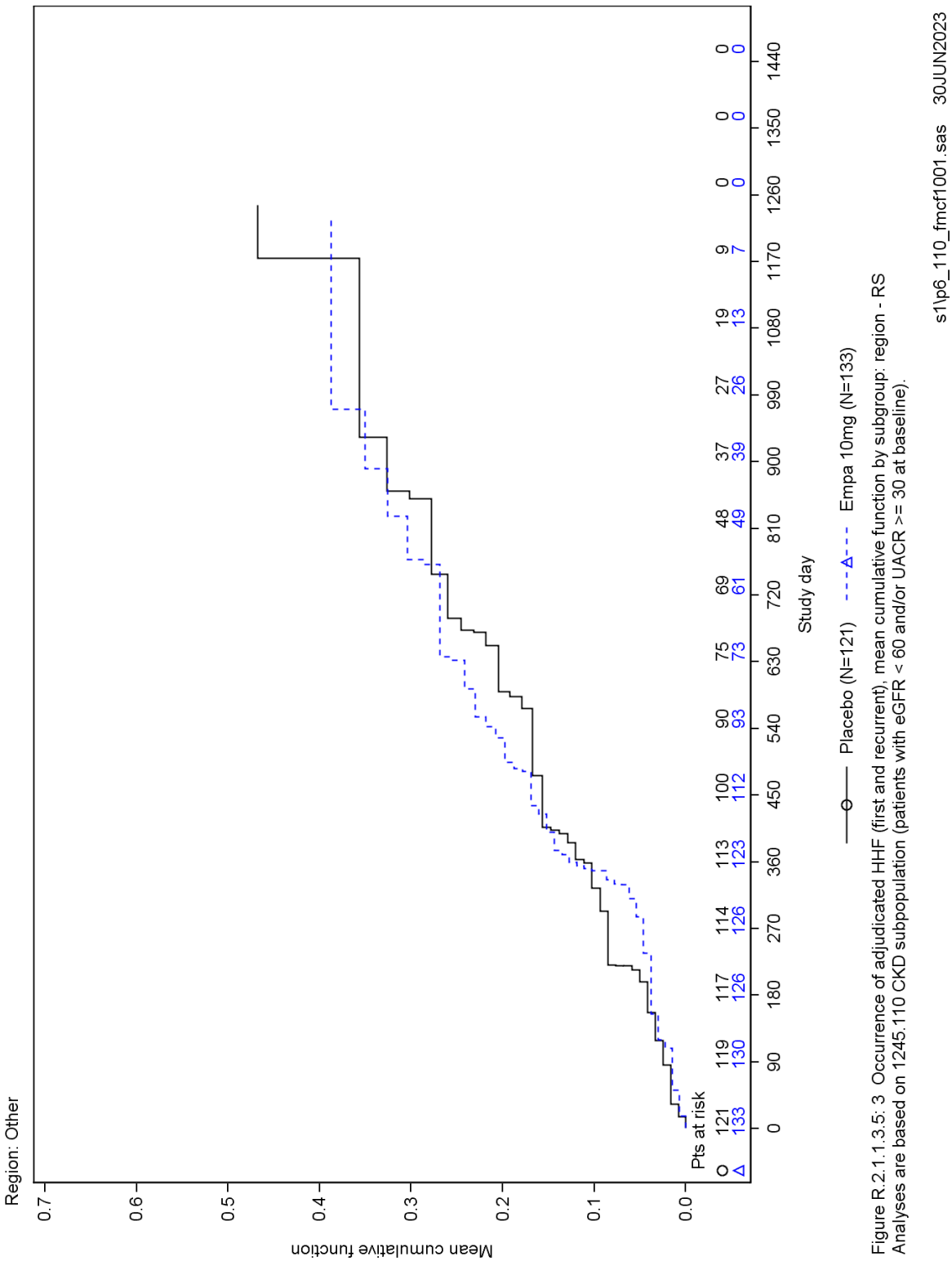


Figure R.2.1.1.3.5: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: region - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.2.1.1.3.6 Time to first occurrence of all-cause hospitalization

Table R.2.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 976 | 48.7 | 33.16 | 2053 | 974 | 47.4 | 31.72 | 0.95 | (0.87,1.04) | 0.2400 | |
| Sex | | | | | | | | | | | | 0.2706 |
| Male | 1065 | 549 | 51.5 | 36.47 | 1094 | 544 | 49.7 | 33.74 | 0.91 | (0.81,1.02) | 0.1073 | |
| Female | 938 | 427 | 45.5 | 29.69 | 959 | 430 | 44.8 | 29.49 | 1.00 | (0.88,1.15) | 0.9638 | |
| Age [years] | | | | | | | | | | | | 0.4504 |
| <65 | 331 | 140 | 42.3 | 26.80 | 313 | 135 | 43.1 | 28.39 | 1.03 | (0.81,1.30) | 0.8064 | |
| >=65 | 1672 | 836 | 50.0 | 34.53 | 1740 | 839 | 48.2 | 32.33 | 0.93 | (0.85,1.03) | 0.1602 | |
| Region | | | | | | | | | | | | 0.4395 |
| North America | 273 | 157 | 57.5 | 42.30 | 274 | 165 | 60.2 | 44.87 | 1.04 | (0.83,1.29) | 0.7356 | |
| Latin America | 511 | 220 | 43.1 | 27.87 | 504 | 204 | 40.5 | 25.90 | 0.93 | (0.77,1.12) | 0.4393 | |
| Europe | 867 | 405 | 46.7 | 31.02 | 894 | 418 | 46.8 | 30.87 | 0.99 | (0.86,1.13) | 0.8416 | |
| Asia | 231 | 126 | 54.5 | 39.97 | 248 | 119 | 48.0 | 30.78 | 0.77 | (0.60,0.99) | 0.0387 | |
| Other | 121 | 68 | 56.2 | 41.93 | 133 | 68 | 51.1 | 38.96 | 0.94 | (0.67,1.32) | 0.7350 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2586 |
| Diabetic | 1046 | 542 | 51.8 | 36.52 | 1082 | 535 | 49.4 | 33.65 | 0.91 | (0.80,1.02) | 0.1038 | |
| Non-Diabetic | 957 | 434 | 45.4 | 29.73 | 971 | 439 | 45.2 | 29.64 | 1.00 | (0.88,1.15) | 0.9559 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0066 |
| <30 | 1087 | 547 | 50.3 | 35.31 | 1094 | 494 | 45.2 | 29.79 | 0.84 | (0.75,0.95) | 0.0067 | |
| >=30 | 916 | 429 | 46.8 | 30.77 | 959 | 480 | 50.1 | 33.98 | 1.08 | (0.95,1.23) | 0.2373 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7529 |
| <130 | 827 | 412 | 49.8 | 35.23 | 853 | 414 | 48.5 | 33.27 | 0.93 | (0.81,1.07) | 0.3103 | |
| >=130 | 1176 | 564 | 48.0 | 31.79 | 1200 | 560 | 46.7 | 30.66 | 0.96 | (0.85,1.08) | 0.4834 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6974 |
| <75 | 936 | 472 | 50.4 | 35.36 | 935 | 473 | 50.6 | 35.15 | 0.98 | (0.86,1.12) | 0.7726 | |
| 75 to <85 | 658 | 313 | 47.6 | 31.60 | 703 | 319 | 45.4 | 29.82 | 0.94 | (0.80,1.10) | 0.4358 | |
| >=85 | 409 | 191 | 46.7 | 30.89 | 415 | 182 | 43.9 | 27.78 | 0.89 | (0.72,1.09) | 0.2421 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.2.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4641 |
| <30 | 161 | 96 | 59.6 | 48.96 | 148 | 91 | 61.5 | 49.81 | 0.98 | (0.73,1.31) | 0.8894 | |
| 30 to <45 | 550 | 311 | 56.5 | 42.70 | 564 | 289 | 51.2 | 36.35 | 0.87 | (0.74,1.02) | 0.0946 | |
| >=45 | 1291 | 569 | 44.1 | 28.21 | 1341 | 594 | 44.3 | 28.38 | 0.99 | (0.88,1.11) | 0.8113 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.1645 |
| Normal (<30) | 766 | 335 | 43.7 | 28.52 | 787 | 361 | 45.9 | 29.74 | 1.06 | (0.91,1.23) | 0.4703 | |
| Microalbuminuria (30 to <=300) | 921 | 463 | 50.3 | 34.25 | 939 | 450 | 47.9 | 32.34 | 0.92 | (0.80,1.04) | 0.1881 | |
| Macroalbuminuria (>300) | 311 | 176 | 56.6 | 43.00 | 318 | 161 | 50.6 | 35.77 | 0.84 | (0.67,1.04) | 0.1019 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2532 |
| Low, moderate or high | 1479 | 666 | 45.0 | 29.31 | 1549 | 698 | 45.1 | 29.00 | 0.98 | (0.89,1.10) | 0.7793 | |
| Very high | 519 | 309 | 59.5 | 46.70 | 495 | 274 | 55.4 | 42.24 | 0.88 | (0.75,1.04) | 0.1222 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9276 |
| No | 412 | 221 | 53.6 | 39.71 | 411 | 215 | 52.3 | 36.11 | 0.94 | (0.78,1.14) | 0.5278 | |
| Yes | 1591 | 755 | 47.5 | 31.63 | 1642 | 759 | 46.2 | 30.66 | 0.95 | (0.86,1.05) | 0.3251 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6708 |
| No | 282 | 139 | 49.3 | 35.28 | 277 | 127 | 45.8 | 31.91 | 0.90 | (0.71,1.15) | 0.4075 | |
| Yes | 1721 | 837 | 48.6 | 32.83 | 1776 | 847 | 47.7 | 31.69 | 0.96 | (0.87,1.05) | 0.3507 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9442 |
| No | 229 | 100 | 43.7 | 27.20 | 250 | 103 | 41.2 | 25.52 | 0.94 | (0.71,1.24) | 0.6591 | |
| Yes | 1774 | 876 | 49.4 | 34.01 | 1803 | 871 | 48.3 | 32.66 | 0.95 | (0.86,1.04) | 0.2817 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.6: 1**

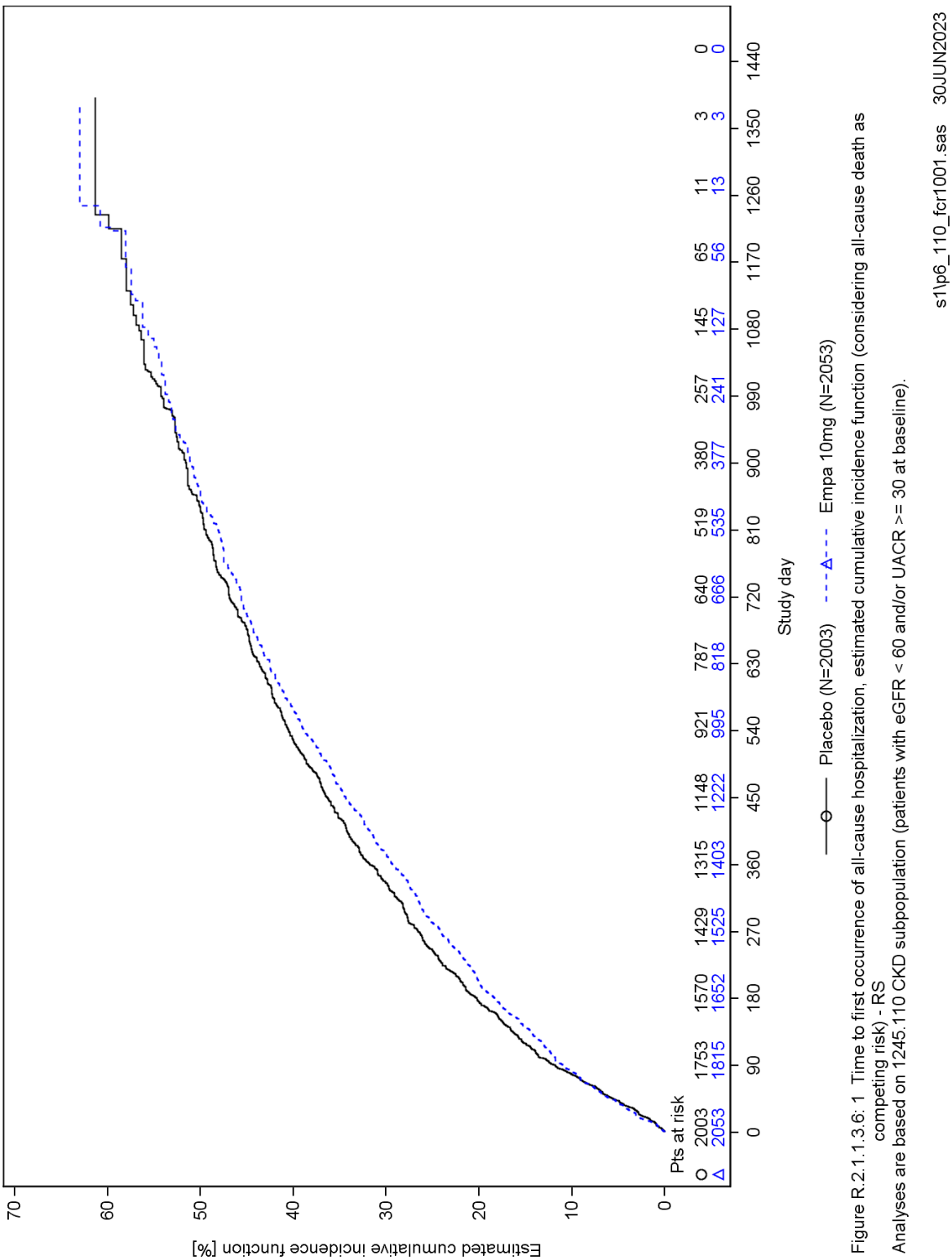


Figure R.2.1.1.3.6: 1 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.6: 2**

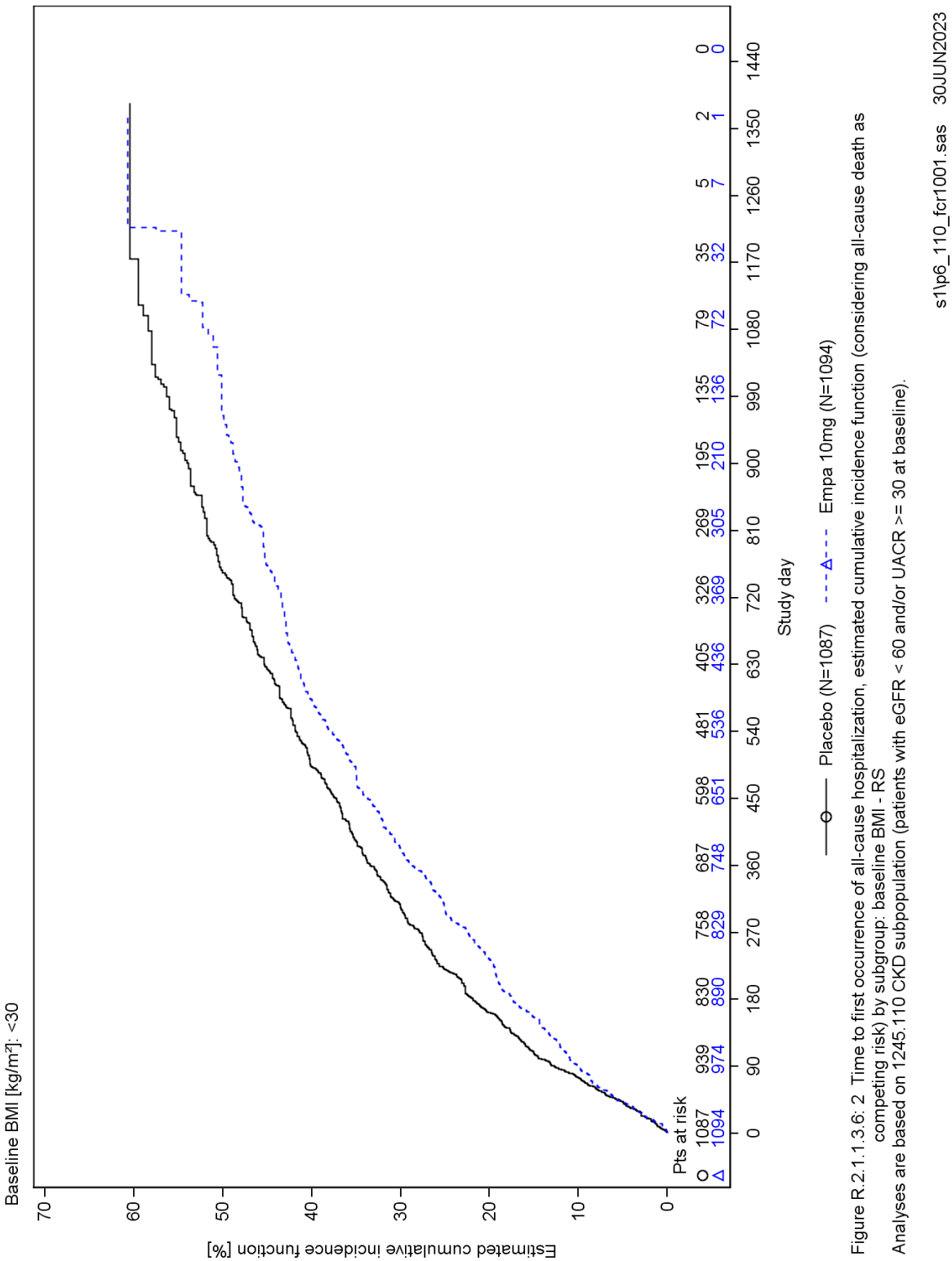


Figure R.2.1.1.3.6: 2 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline BMI - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.6: 2**

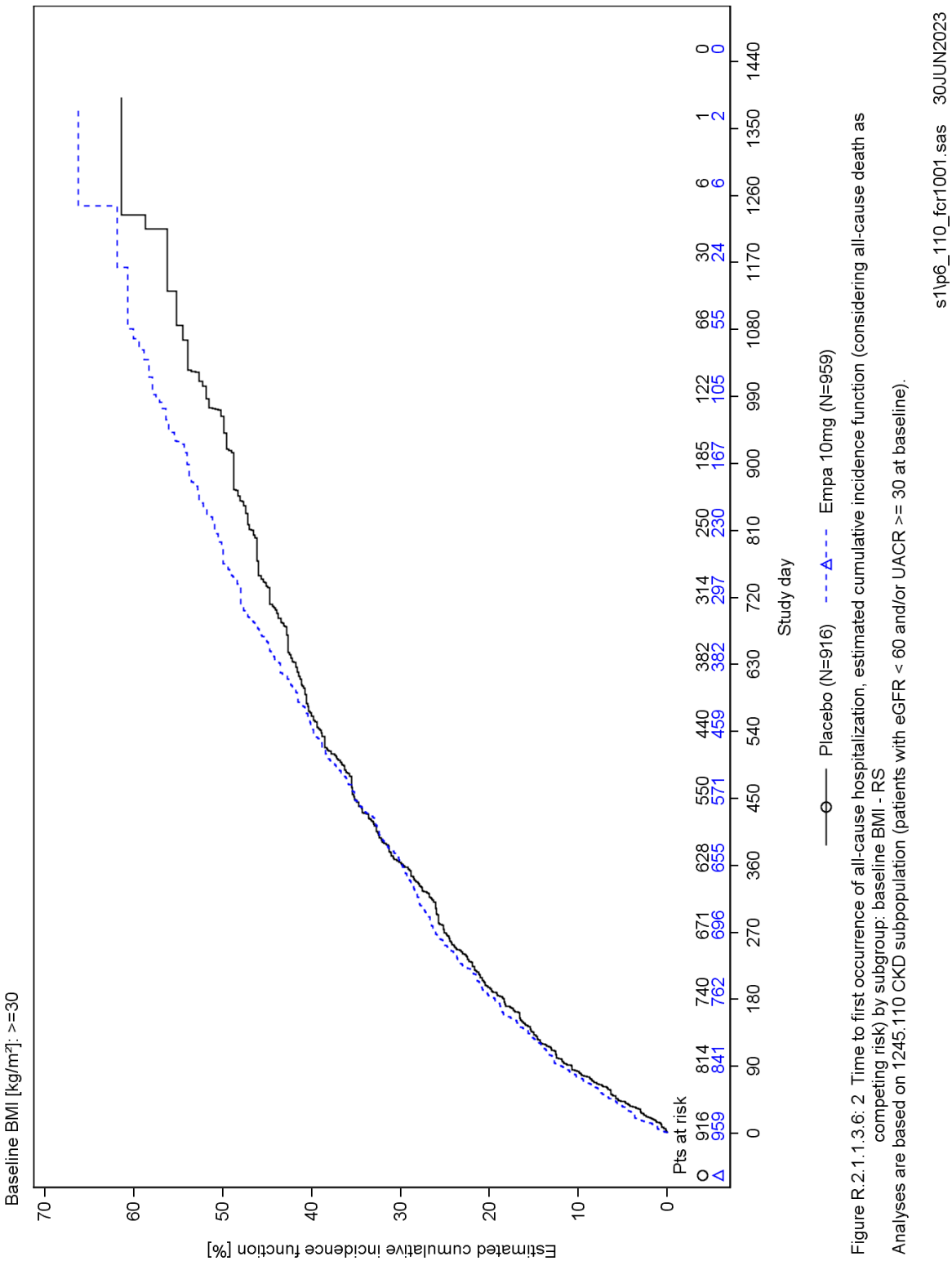


Figure R.2.1.1.3.6: 2 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline BMI - RS

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.2.1.1.3.7 Time to occurrence of all-cause hospitalizations (first and recurrent)

Table R.2.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 2003 | 976 | 48.7 | 2104 | 50.56 | 2053 | 974 | 47.4 | 2035 | 47.82 | 0.94 | (0.85,1.04) | 0.2372 | |
| Sex | | | | | | | | | | | | | | 0.8949 |
| Male | 1065 | 549 | 51.5 | 1203 | 54.81 | 1094 | 544 | 49.7 | 1200 | 53.01 | 0.95 | (0.82,1.09) | 0.4309 | |
| Female | 938 | 427 | 45.5 | 901 | 45.82 | 959 | 430 | 44.8 | 835 | 41.92 | 0.93 | (0.80,1.09) | 0.3722 | |
| Age [years] | | | | | | | | | | | | | | 0.4179 |
| <65 | 331 | 140 | 42.3 | 306 | 43.91 | 313 | 135 | 43.1 | 283 | 43.26 | 1.04 | (0.80,1.35) | 0.7838 | |
| >=65 | 1672 | 836 | 50.0 | 1798 | 51.90 | 1740 | 839 | 48.2 | 1752 | 48.65 | 0.92 | (0.83,1.03) | 0.1502 | |
| Region | | | | | | | | | | | | | | 0.2133 |
| North America | 273 | 157 | 57.5 | 401 | 67.02 | 274 | 165 | 60.2 | 416 | 69.95 | 1.14 | (0.88,1.48) | 0.3038 | |
| Latin America | 511 | 220 | 43.1 | 380 | 37.85 | 504 | 204 | 40.5 | 341 | 34.56 | 0.88 | (0.71,1.10) | 0.2724 | |
| Europe | 867 | 405 | 46.7 | 879 | 48.01 | 894 | 418 | 46.8 | 864 | 45.87 | 0.97 | (0.83,1.13) | 0.6609 | |
| Asia | 231 | 126 | 54.5 | 283 | 58.44 | 248 | 119 | 48.0 | 248 | 46.54 | 0.72 | (0.54,0.97) | 0.0298 | |
| Other | 121 | 68 | 56.2 | 161 | 66.07 | 133 | 68 | 51.1 | 166 | 64.34 | 0.99 | (0.67,1.46) | 0.9661 | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2918 |
| Diabetic | 1046 | 542 | 51.8 | 1240 | 57.08 | 1082 | 535 | 49.4 | 1142 | 51.09 | 0.89 | (0.78,1.03) | 0.1164 | |
| Non-Diabetic | 957 | 434 | 45.4 | 864 | 43.44 | 971 | 439 | 45.2 | 893 | 44.20 | 1.00 | (0.86,1.16) | 0.9898 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0146 |
| <30 | 1087 | 547 | 50.3 | 1133 | 51.65 | 1094 | 494 | 45.2 | 1007 | 45.01 | 0.84 | (0.73,0.96) | 0.0127 | |
| >=30 | 916 | 429 | 46.8 | 971 | 49.35 | 959 | 480 | 50.1 | 1028 | 50.93 | 1.08 | (0.93,1.25) | 0.3149 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5627 |
| <130 | 827 | 412 | 49.8 | 906 | 53.73 | 853 | 414 | 48.5 | 896 | 50.91 | 0.97 | (0.83,1.14) | 0.7384 | |
| >=130 | 1176 | 564 | 48.0 | 1198 | 48.40 | 1200 | 560 | 46.7 | 1139 | 45.64 | 0.92 | (0.80,1.05) | 0.2005 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9091 |
| <75 | 936 | 472 | 50.4 | 1086 | 55.84 | 935 | 473 | 50.6 | 1041 | 53.75 | 0.96 | (0.82,1.11) | 0.5390 | |
| 75 to <85 | 658 | 313 | 47.6 | 649 | 47.16 | 703 | 319 | 45.4 | 631 | 43.66 | 0.95 | (0.79,1.13) | 0.5468 | |
| >=85 | 409 | 191 | 46.7 | 369 | 43.92 | 415 | 182 | 43.9 | 363 | 41.56 | 0.90 | (0.71,1.13) | 0.3696 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline LVEF, baseline diabetes status, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.2.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5895 |
| <30 | 161 | 96 | 59.6 | 225 | 74.80 | 148 | 91 | 61.5 | 249 | 84.90 | 1.12 | (0.79,1.59) | 0.5134 | |
| 30 to <45 | 550 | 311 | 56.5 | 690 | 60.12 | 564 | 289 | 51.2 | 633 | 54.17 | 0.93 | (0.77,1.12) | 0.4302 | |
| >=45 | 1291 | 569 | 44.1 | 1189 | 43.87 | 1341 | 594 | 44.3 | 1153 | 41.27 | 0.93 | (0.82,1.06) | 0.2625 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2411 |
| Normal (<30) | 766 | 335 | 43.7 | 722 | 44.89 | 787 | 361 | 45.9 | 729 | 44.08 | 1.06 | (0.90,1.25) | 0.4950 | |
| Microalbuminuria (30 to <=300) | 921 | 463 | 50.3 | 956 | 50.20 | 939 | 450 | 47.9 | 950 | 48.75 | 0.91 | (0.78,1.05) | 0.2002 | |
| Macroalbuminuria (>300) | 311 | 176 | 56.6 | 420 | 65.84 | 318 | 161 | 50.6 | 353 | 55.68 | 0.85 | (0.66,1.09) | 0.1923 | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5196 |
| Low, moderate or high | 1479 | 666 | 45.0 | 1390 | 44.78 | 1549 | 698 | 45.1 | 1370 | 42.16 | 0.93 | (0.83,1.05) | 0.2677 | |
| Very high | 519 | 309 | 59.5 | 710 | 67.85 | 495 | 274 | 55.4 | 662 | 67.07 | 1.01 | (0.83,1.22) | 0.9432 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5345 |
| No | 412 | 221 | 53.6 | 503 | 59.51 | 411 | 215 | 52.3 | 500 | 58.18 | 1.00 | (0.80,1.24) | 0.9944 | |
| Yes | 1591 | 755 | 47.5 | 1601 | 48.28 | 1642 | 759 | 46.2 | 1535 | 45.20 | 0.92 | (0.82,1.04) | 0.1788 | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.0586 |
| No | 282 | 139 | 49.3 | 334 | 58.87 | 277 | 127 | 45.8 | 249 | 45.63 | 0.74 | (0.56,0.97) | 0.0291 | |
| Yes | 1721 | 837 | 48.6 | 1770 | 49.25 | 1776 | 847 | 47.7 | 1786 | 48.14 | 0.98 | (0.88,1.09) | 0.7096 | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4854 |
| No | 229 | 100 | 43.7 | 193 | 39.61 | 250 | 103 | 41.2 | 169 | 32.97 | 0.85 | (0.62,1.16) | 0.2962 | |
| Yes | 1774 | 876 | 49.4 | 1911 | 52.01 | 1803 | 871 | 48.3 | 1866 | 49.85 | 0.95 | (0.85,1.06) | 0.3643 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline LVEF, baseline diabetes status, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.7: 1**

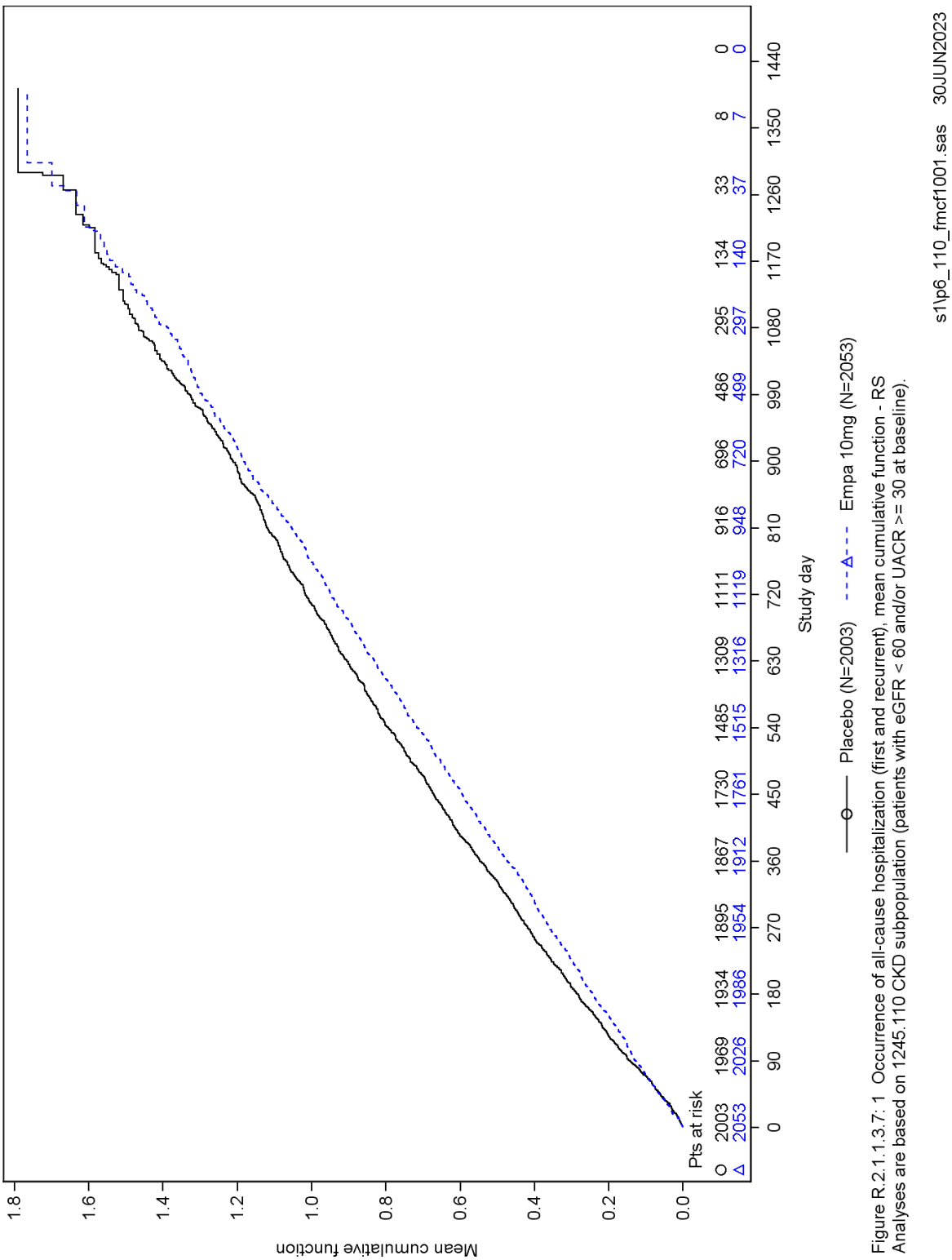


Figure R.2.1.1.3.7: 1 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.7: 2**

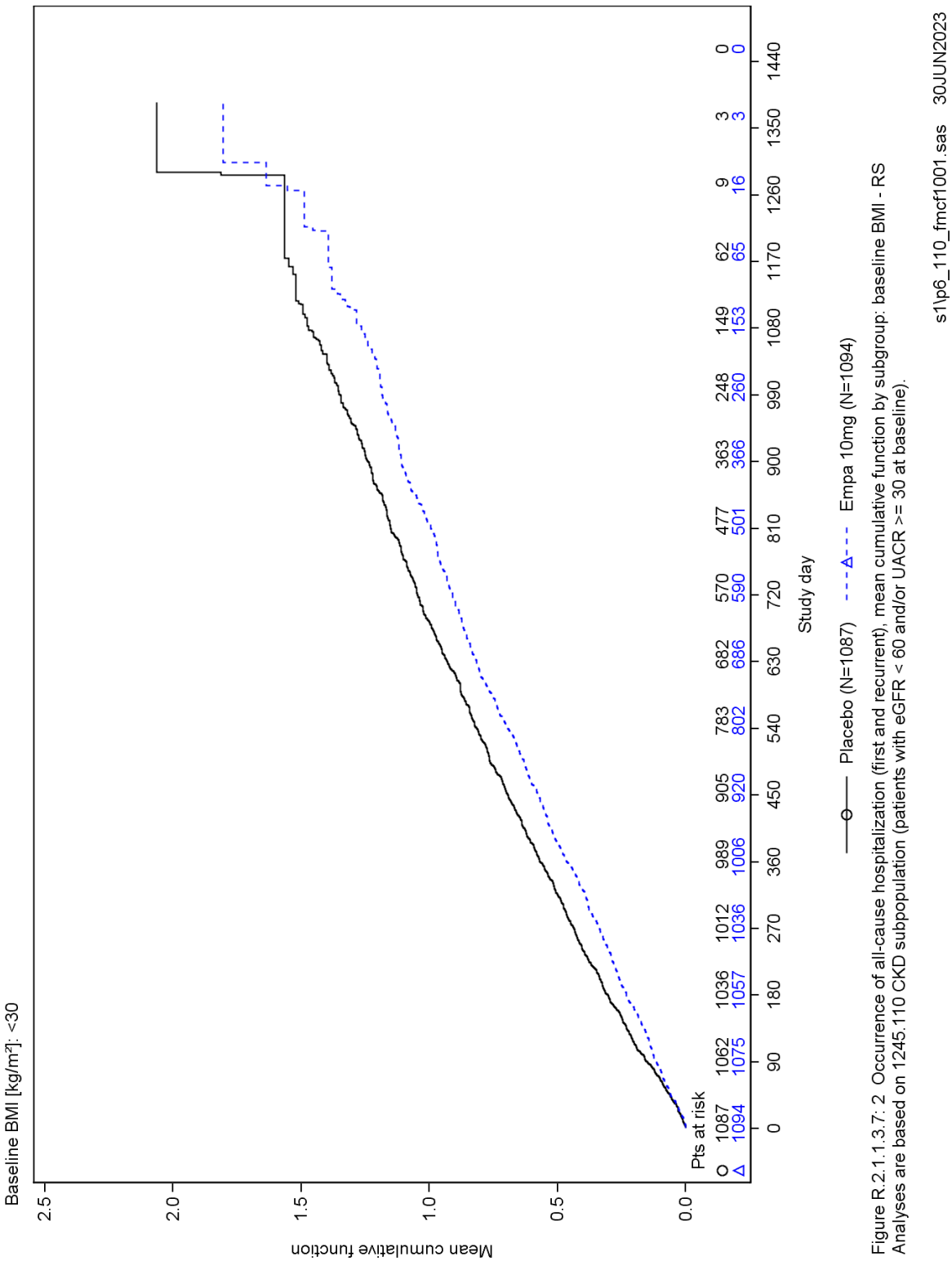


Figure R.2.1.1.3.7: 2 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: baseline BMI - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.2.1.1.3.7: 2**

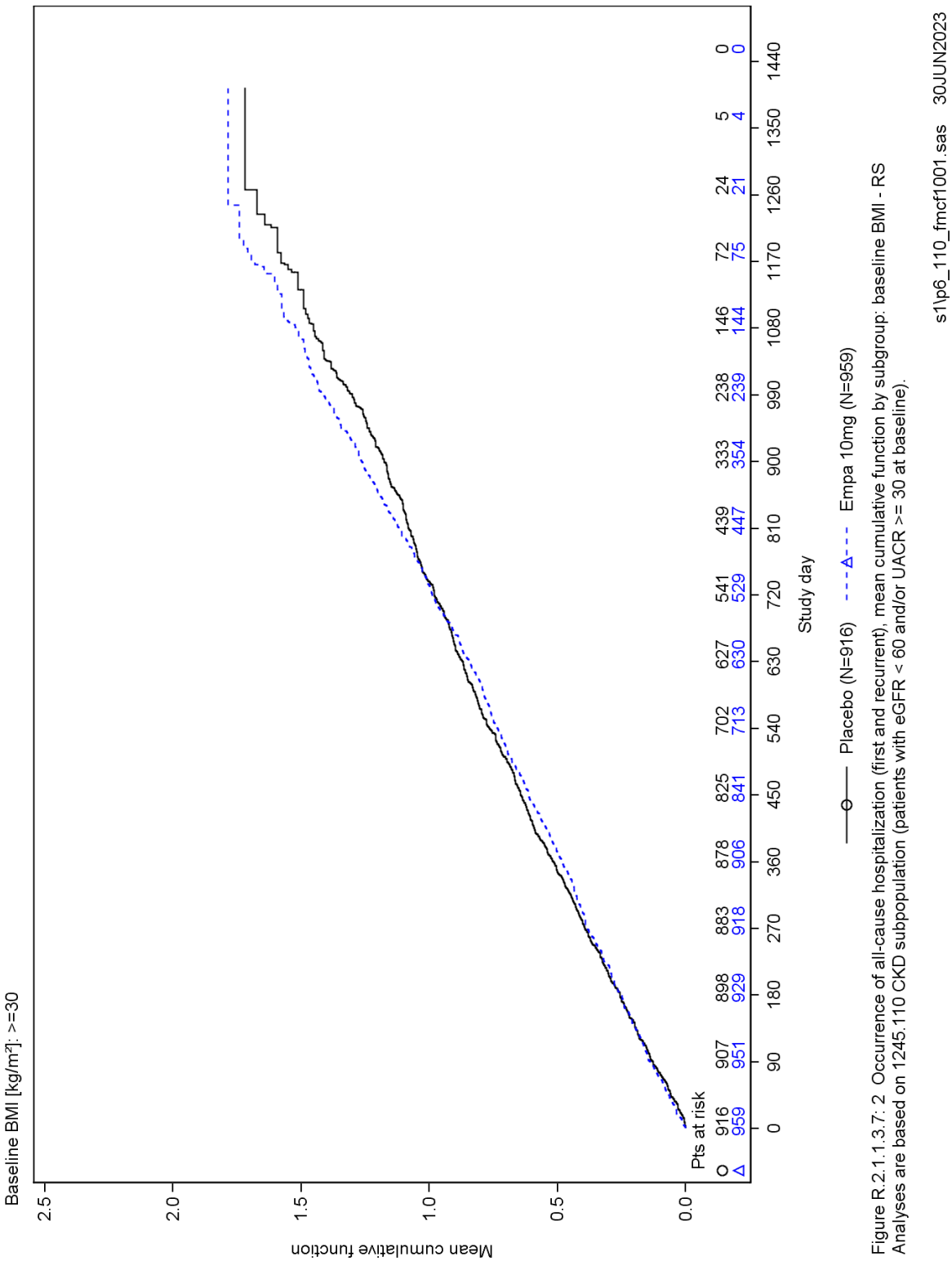


Figure R.2.1.1.3.7: 2 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: baseline BMI - RS
Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.2.1.2**

R.2.1.2.1 Responder analyses based on last value during planned treatment period

R.2.1.2.1.1 EQ-VAS responder analysis (15 points)

Table R.2.1.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1913 | 358 | 18.7 | 1968 | 337 | 17.1 | 0.89 | (0.78,1.02) | 0.0950 | 0.89 | (0.75,1.06) | |
| Sex | | | | | | | | | | | | 0.9992 |
| Male | 1020 | 196 | 19.2 | 1050 | 188 | 17.9 | 0.89 | (0.74,1.07) | 0.2195 | 0.93 | (0.74,1.17) | |
| Female | 893 | 162 | 18.1 | 918 | 149 | 16.2 | 0.89 | (0.73,1.09) | 0.2597 | 0.84 | (0.65,1.09) | |
| Age [years] | | | | | | | | | | | | 0.4058 |
| <65 | 312 | 46 | 14.7 | 303 | 43 | 14.2 | 0.75 | (0.49,1.15) | 0.1888 | 1.00 | (0.62,1.59) | |
| >=65 | 1601 | 312 | 19.5 | 1665 | 294 | 17.7 | 0.91 | (0.79,1.05) | 0.1820 | 0.87 | (0.73,1.05) | |
| Region | | | | | | | | | | | | 0.1505 |
| North America | 263 | 50 | 19.0 | 259 | 64 | 24.7 | 1.27 | (0.92,1.75) | 0.1526 | 1.32 | (0.86,2.04) | |
| Latin America | 481 | 70 | 14.6 | 480 | 68 | 14.2 | 0.84 | (0.61,1.17) | 0.3021 | 0.99 | (0.68,1.44) | |
| Europe | 838 | 178 | 21.2 | 867 | 156 | 18.0 | 0.85 | (0.70,1.02) | 0.0850 | 0.79 | (0.61,1.01) | |
| Asia | 223 | 39 | 17.5 | 239 | 36 | 15.1 | 0.89 | (0.59,1.33) | 0.5639 | 0.91 | (0.54,1.51) | |
| Other | 108 | 21 | 19.4 | 123 | 13 | 10.6 | 0.58 | (0.31,1.08) | 0.0875 | 0.51 | (0.24,1.10) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.8780 |
| Diabetic | 996 | 186 | 18.7 | 1032 | 174 | 16.9 | 0.90 | (0.75,1.08) | 0.2628 | 0.88 | (0.69,1.12) | |
| Non-Diabetic | 917 | 172 | 18.8 | 936 | 163 | 17.4 | 0.88 | (0.72,1.07) | 0.2063 | 0.90 | (0.70,1.15) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2817 |
| <30 | 1033 | 183 | 17.7 | 1048 | 178 | 17.0 | 0.96 | (0.80,1.15) | 0.6336 | 0.93 | (0.74,1.18) | |
| >=30 | 880 | 175 | 19.9 | 920 | 159 | 17.3 | 0.83 | (0.68,1.00) | 0.0554 | 0.84 | (0.66,1.08) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8546 |
| <130 | 793 | 143 | 18.0 | 820 | 134 | 16.3 | 0.91 | (0.73,1.12) | 0.3589 | 0.89 | (0.68,1.16) | |
| >=130 | 1120 | 215 | 19.2 | 1148 | 203 | 17.7 | 0.88 | (0.74,1.05) | 0.1620 | 0.89 | (0.71,1.11) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4379 |
| <75 | 904 | 176 | 19.5 | 895 | 168 | 18.8 | 0.97 | (0.81,1.17) | 0.7831 | 0.97 | (0.76,1.24) | |
| 75 to <85 | 620 | 120 | 19.4 | 677 | 107 | 15.8 | 0.82 | (0.65,1.03) | 0.0844 | 0.76 | (0.56,1.02) | |
| >=85 | 389 | 62 | 15.9 | 396 | 62 | 15.7 | 0.82 | (0.58,1.16) | 0.2690 | 0.95 | (0.63,1.41) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.2.1.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8290 |
| <30 | 149 | 30 | 20.1 | 139 | 24 | 17.3 | 0.90 | (0.56,1.45) | 0.6530 | 0.96 | (0.51,1.79) | |
| 30 to <45 | 531 | 106 | 20.0 | 543 | 101 | 18.6 | 0.95 | (0.75,1.20) | 0.6577 | 0.89 | (0.65,1.22) | |
| >=45 | 1232 | 222 | 18.0 | 1286 | 212 | 16.5 | 0.86 | (0.73,1.03) | 0.0952 | 0.88 | (0.71,1.09) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4713 |
| Normal (<30) | 738 | 147 | 19.9 | 764 | 145 | 19.0 | 0.98 | (0.80,1.20) | 0.8388 | 0.96 | (0.73,1.25) | |
| Microalbuminuria (30 to <=300) | 873 | 155 | 17.8 | 891 | 141 | 15.8 | 0.82 | (0.66,1.01) | 0.0575 | 0.84 | (0.65,1.09) | |
| Macroalbuminuria (>300) | 298 | 55 | 18.5 | 304 | 50 | 16.4 | 0.90 | (0.64,1.26) | 0.5400 | 0.86 | (0.55,1.34) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7170 |
| Low, moderate or high | 1414 | 258 | 18.2 | 1491 | 256 | 17.2 | 0.91 | (0.78,1.06) | 0.2199 | 0.91 | (0.75,1.11) | |
| Very high | 495 | 99 | 20.0 | 468 | 80 | 17.1 | 0.86 | (0.66,1.11) | 0.2467 | 0.83 | (0.59,1.17) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6714 |
| No | 388 | 78 | 20.1 | 391 | 65 | 16.6 | 0.84 | (0.63,1.13) | 0.2522 | 0.78 | (0.54,1.15) | |
| Yes | 1525 | 280 | 18.4 | 1577 | 272 | 17.2 | 0.91 | (0.78,1.05) | 0.1970 | 0.92 | (0.76,1.11) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4598 |
| No | 261 | 56 | 21.5 | 258 | 56 | 21.7 | 1.00 | (0.72,1.37) | 0.9896 | 0.96 | (0.62,1.48) | |
| Yes | 1652 | 302 | 18.3 | 1710 | 281 | 16.4 | 0.87 | (0.75,1.01) | 0.0718 | 0.88 | (0.73,1.06) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.0981 |
| No | 219 | 45 | 20.5 | 237 | 32 | 13.5 | 0.65 | (0.43,0.97) | 0.0351 | 0.59 | (0.35,0.99) | |
| Yes | 1694 | 313 | 18.5 | 1731 | 305 | 17.6 | 0.93 | (0.81,1.07) | 0.3105 | 0.94 | (0.78,1.12) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.2.1.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1913 | 394 | 20.6 | 1968 | 438 | 22.3 | 1.05 | (0.94,1.18) | 0.3800 | 1.13 | (0.94,1.35) | |
| Sex | | | | | | | | | | | | 0.7701 |
| Male | 1020 | 196 | 19.2 | 1050 | 214 | 20.4 | 1.03 | (0.88,1.22) | 0.6853 | 1.07 | (0.84,1.37) | |
| Female | 893 | 198 | 22.2 | 918 | 224 | 24.4 | 1.07 | (0.91,1.25) | 0.4025 | 1.19 | (0.92,1.53) | |
| Age [years] | | | | | | | | | | | | 0.1263 |
| <65 | 312 | 73 | 23.4 | 303 | 93 | 30.7 | 1.26 | (0.98,1.61) | 0.0723 | 1.60 | (1.04,2.45) | |
| >=65 | 1601 | 321 | 20.0 | 1665 | 345 | 20.7 | 1.01 | (0.89,1.15) | 0.8895 | 1.05 | (0.86,1.27) | |
| Region | | | | | | | | | | | | 0.8728 |
| North America | 263 | 56 | 21.3 | 259 | 43 | 16.6 | 0.90 | (0.65,1.25) | 0.5320 | 0.81 | (0.49,1.35) | |
| Latin America | 481 | 136 | 28.3 | 480 | 158 | 32.9 | 1.07 | (0.89,1.30) | 0.4694 | 1.27 | (0.92,1.75) | |
| Europe | 838 | 146 | 17.4 | 867 | 165 | 19.0 | 1.10 | (0.91,1.33) | 0.3107 | 1.18 | (0.90,1.56) | |
| Asia | 223 | 35 | 15.7 | 239 | 43 | 18.0 | 1.03 | (0.72,1.48) | 0.8742 | 1.04 | (0.60,1.81) | |
| Other | 108 | 21 | 19.4 | 123 | 29 | 23.6 | 0.98 | (0.62,1.56) | 0.9462 | 1.00 | (0.48,2.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.0066 |
| Diabetic | 996 | 212 | 21.3 | 1032 | 271 | 26.3 | 1.20 | (1.04,1.40) | 0.0151 | 1.46 | (1.15,1.86) | |
| Non-Diabetic | 917 | 182 | 19.8 | 936 | 167 | 17.8 | 0.87 | (0.73,1.04) | 0.1350 | 0.82 | (0.63,1.06) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1653 |
| <30 | 1033 | 208 | 20.1 | 1048 | 196 | 18.7 | 0.97 | (0.82,1.14) | 0.7043 | 0.96 | (0.75,1.23) | |
| >=30 | 880 | 186 | 21.1 | 920 | 242 | 26.3 | 1.14 | (0.97,1.34) | 0.1083 | 1.33 | (1.04,1.72) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8609 |
| <130 | 793 | 160 | 20.2 | 820 | 175 | 21.3 | 1.06 | (0.89,1.27) | 0.4861 | 1.10 | (0.84,1.45) | |
| >=130 | 1120 | 234 | 20.9 | 1148 | 263 | 22.9 | 1.04 | (0.90,1.21) | 0.5747 | 1.14 | (0.91,1.44) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2552 |
| <75 | 904 | 180 | 19.9 | 895 | 189 | 21.1 | 0.95 | (0.80,1.13) | 0.5491 | 0.96 | (0.74,1.25) | |
| 75 to <85 | 620 | 127 | 20.5 | 677 | 149 | 22.0 | 1.11 | (0.92,1.35) | 0.2785 | 1.24 | (0.91,1.69) | |
| >=85 | 389 | 87 | 22.4 | 396 | 100 | 25.3 | 1.19 | (0.94,1.52) | 0.1474 | 1.37 | (0.93,2.00) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.2.1.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1112 |
| <30 | 149 | 19 | 12.8 | 139 | 38 | 27.3 | 1.71 | (1.07,2.75) | 0.0263 | 2.45 | (1.23,4.89) | |
| 30 to <45 | 531 | 114 | 21.5 | 543 | 126 | 23.2 | 1.00 | (0.81,1.24) | 0.9893 | 1.08 | (0.78,1.51) | |
| >=45 | 1232 | 261 | 21.2 | 1286 | 274 | 21.3 | 1.03 | (0.89,1.18) | 0.7123 | 1.06 | (0.85,1.32) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0698 |
| Normal (<30) | 738 | 135 | 18.3 | 764 | 158 | 20.7 | 1.10 | (0.90,1.34) | 0.3713 | 1.19 | (0.89,1.59) | |
| Microalbuminuria (30 to <=300) | 873 | 194 | 22.2 | 891 | 188 | 21.1 | 0.93 | (0.79,1.09) | 0.3568 | 0.92 | (0.71,1.19) | |
| Macroalbuminuria (>300) | 298 | 65 | 21.8 | 304 | 89 | 29.3 | 1.32 | (1.01,1.72) | 0.0394 | 1.71 | (1.11,2.63) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2850 |
| Low, moderate or high | 1414 | 294 | 20.8 | 1491 | 313 | 21.0 | 1.01 | (0.88,1.15) | 0.8974 | 1.04 | (0.85,1.28) | |
| Very high | 495 | 100 | 20.2 | 468 | 122 | 26.1 | 1.16 | (0.93,1.45) | 0.1835 | 1.38 | (0.97,1.95) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7307 |
| No | 388 | 77 | 19.8 | 391 | 85 | 21.7 | 1.10 | (0.84,1.42) | 0.4960 | 1.18 | (0.79,1.76) | |
| Yes | 1525 | 317 | 20.8 | 1577 | 353 | 22.4 | 1.04 | (0.92,1.18) | 0.5342 | 1.11 | (0.92,1.36) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5349 |
| No | 261 | 51 | 19.5 | 258 | 49 | 19.0 | 0.95 | (0.67,1.34) | 0.7709 | 0.96 | (0.58,1.57) | |
| Yes | 1652 | 343 | 20.8 | 1710 | 389 | 22.7 | 1.07 | (0.95,1.20) | 0.2941 | 1.15 | (0.95,1.39) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.0719 |
| No | 219 | 48 | 21.9 | 237 | 44 | 18.6 | 0.79 | (0.57,1.10) | 0.1603 | 0.77 | (0.45,1.29) | |
| Yes | 1694 | 346 | 20.4 | 1731 | 394 | 22.8 | 1.09 | (0.97,1.23) | 0.1660 | 1.18 | (0.98,1.43) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**R.2.1.2.1.2**

R.2.1.2.1.2 KCCQ-OSS responder analysis (5 points)

Table R.2.1.2.1.2: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -5 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1912 | 579 | 30.3 | 1965 | 511 | 26.0 | 0.86 | (0.78,0.95) | 0.0028 | 0.80 | (0.69,0.93) | |
| Sex | | | | | | | | | | | | 0.5595 |
| Male | 1019 | 321 | 31.5 | 1047 | 290 | 27.7 | 0.88 | (0.78,1.01) | 0.0620 | 0.83 | (0.68,1.01) | |
| Female | 893 | 258 | 28.9 | 918 | 221 | 24.1 | 0.83 | (0.72,0.97) | 0.0165 | 0.77 | (0.62,0.96) | |
| Age [years] | | | | | | | | | | | | 0.9380 |
| <65 | 313 | 74 | 23.6 | 302 | 62 | 20.5 | 0.85 | (0.63,1.14) | 0.2688 | 0.80 | (0.54,1.18) | |
| >=65 | 1599 | 505 | 31.6 | 1663 | 449 | 27.0 | 0.86 | (0.77,0.95) | 0.0044 | 0.80 | (0.68,0.93) | |
| Region | | | | | | | | | | | | 0.7451 |
| North America | 264 | 78 | 29.5 | 260 | 72 | 27.7 | 0.91 | (0.70,1.19) | 0.4911 | 0.87 | (0.59,1.28) | |
| Latin America | 482 | 117 | 24.3 | 479 | 93 | 19.4 | 0.81 | (0.64,1.03) | 0.0810 | 0.75 | (0.55,1.03) | |
| Europe | 838 | 270 | 32.2 | 867 | 250 | 28.8 | 0.89 | (0.78,1.03) | 0.1179 | 0.85 | (0.68,1.04) | |
| Asia | 220 | 76 | 34.5 | 237 | 59 | 24.9 | 0.74 | (0.56,0.98) | 0.0334 | 0.64 | (0.42,0.97) | |
| Other | 108 | 38 | 35.2 | 122 | 37 | 30.3 | 0.91 | (0.64,1.30) | 0.6166 | 0.87 | (0.49,1.54) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9169 |
| Diabetic | 994 | 288 | 29.0 | 1029 | 259 | 25.2 | 0.86 | (0.75,0.98) | 0.0295 | 0.80 | (0.65,0.98) | |
| Non-Diabetic | 918 | 291 | 31.7 | 936 | 252 | 26.9 | 0.87 | (0.75,1.00) | 0.0429 | 0.81 | (0.66,0.99) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7967 |
| <30 | 1028 | 315 | 30.6 | 1046 | 280 | 26.8 | 0.87 | (0.76,0.99) | 0.0416 | 0.82 | (0.67,0.99) | |
| >=30 | 884 | 264 | 29.9 | 919 | 231 | 25.1 | 0.85 | (0.73,0.98) | 0.0278 | 0.79 | (0.64,0.97) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0364 |
| <130 | 793 | 218 | 27.5 | 819 | 223 | 27.2 | 0.98 | (0.84,1.14) | 0.7810 | 0.97 | (0.77,1.22) | |
| >=130 | 1119 | 361 | 32.3 | 1146 | 288 | 25.1 | 0.79 | (0.69,0.90) | 0.0002 | 0.70 | (0.58,0.85) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3470 |
| <75 | 901 | 264 | 29.3 | 896 | 244 | 27.2 | 0.93 | (0.81,1.07) | 0.3248 | 0.90 | (0.73,1.11) | |
| 75 to <85 | 622 | 190 | 30.5 | 674 | 167 | 24.8 | 0.80 | (0.67,0.95) | 0.0106 | 0.72 | (0.56,0.93) | |
| >=85 | 389 | 125 | 32.1 | 395 | 100 | 25.3 | 0.81 | (0.65,1.01) | 0.0649 | 0.73 | (0.53,1.01) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.2.1.2.1.2: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -5 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2828 |
| <30 | 150 | 55 | 36.7 | 138 | 33 | 23.9 | 0.66 | (0.47,0.94) | 0.0215 | 0.53 | (0.31,0.91) | |
| 30 to <45 | 530 | 176 | 33.2 | 541 | 160 | 29.6 | 0.91 | (0.77,1.08) | 0.2871 | 0.87 | (0.66,1.13) | |
| >=45 | 1231 | 348 | 28.3 | 1286 | 318 | 24.7 | 0.87 | (0.76,0.98) | 0.0268 | 0.81 | (0.68,0.98) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4405 |
| Normal (<30) | 738 | 224 | 30.4 | 761 | 210 | 27.6 | 0.92 | (0.78,1.07) | 0.2737 | 0.88 | (0.70,1.10) | |
| Microalbuminuria (30 to <=300) | 873 | 260 | 29.8 | 890 | 222 | 24.9 | 0.85 | (0.73,0.98) | 0.0264 | 0.78 | (0.63,0.97) | |
| Macroalbuminuria (>300) | 297 | 93 | 31.3 | 305 | 75 | 24.6 | 0.76 | (0.59,0.97) | 0.0294 | 0.66 | (0.46,0.96) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3046 |
| Low, moderate or high | 1413 | 398 | 28.2 | 1489 | 373 | 25.1 | 0.89 | (0.79,1.00) | 0.0536 | 0.85 | (0.72,1.00) | |
| Very high | 495 | 179 | 36.2 | 467 | 134 | 28.7 | 0.80 | (0.67,0.95) | 0.0118 | 0.70 | (0.53,0.92) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5403 |
| No | 389 | 125 | 32.1 | 388 | 115 | 29.6 | 0.91 | (0.74,1.12) | 0.3654 | 0.87 | (0.63,1.18) | |
| Yes | 1523 | 454 | 29.8 | 1577 | 396 | 25.1 | 0.85 | (0.76,0.95) | 0.0038 | 0.79 | (0.67,0.93) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.2072 |
| No | 260 | 87 | 33.5 | 258 | 65 | 25.2 | 0.74 | (0.57,0.96) | 0.0219 | 0.63 | (0.43,0.94) | |
| Yes | 1652 | 492 | 29.8 | 1707 | 446 | 26.1 | 0.88 | (0.79,0.98) | 0.0209 | 0.83 | (0.71,0.97) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.5061 |
| No | 218 | 61 | 28.0 | 237 | 53 | 22.4 | 0.78 | (0.57,1.07) | 0.1192 | 0.70 | (0.46,1.09) | |
| Yes | 1694 | 518 | 30.6 | 1728 | 458 | 26.5 | 0.87 | (0.79,0.97) | 0.0096 | 0.82 | (0.70,0.95) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.2.1.2.1.2: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 5 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1912 | 774 | 40.5 | 1965 | 905 | 46.1 | 1.13 | (1.05,1.21) | 0.0006 | 1.29 | (1.12,1.48) | |
| Sex | | | | | | | | | | | | 0.4579 |
| Male | 1019 | 384 | 37.7 | 1047 | 456 | 43.6 | 1.16 | (1.05,1.28) | 0.0037 | 1.32 | (1.10,1.60) | |
| Female | 893 | 390 | 43.7 | 918 | 449 | 48.9 | 1.10 | (1.00,1.21) | 0.0508 | 1.25 | (1.02,1.54) | |
| Age [years] | | | | | | | | | | | | 0.0740 |
| <65 | 313 | 161 | 51.4 | 302 | 154 | 51.0 | 1.00 | (0.86,1.15) | 0.9707 | 1.02 | (0.72,1.44) | |
| >=65 | 1599 | 613 | 38.3 | 1663 | 751 | 45.2 | 1.16 | (1.07,1.25) | 0.0002 | 1.35 | (1.16,1.57) | |
| Region | | | | | | | | | | | | 0.5840 |
| North America | 264 | 104 | 39.4 | 260 | 108 | 41.5 | 1.11 | (0.91,1.35) | 0.3015 | 1.22 | (0.84,1.79) | |
| Latin America | 482 | 243 | 50.4 | 479 | 278 | 58.0 | 1.13 | (1.01,1.27) | 0.0280 | 1.39 | (1.05,1.84) | |
| Europe | 838 | 320 | 38.2 | 867 | 369 | 42.6 | 1.10 | (0.99,1.23) | 0.0819 | 1.22 | (0.99,1.50) | |
| Asia | 220 | 61 | 27.7 | 237 | 92 | 38.8 | 1.35 | (1.05,1.74) | 0.0193 | 1.63 | (1.07,2.47) | |
| Other | 108 | 46 | 42.6 | 122 | 58 | 47.5 | 1.01 | (0.78,1.31) | 0.9459 | 1.06 | (0.60,1.87) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.5095 |
| Diabetic | 994 | 413 | 41.5 | 1029 | 491 | 47.7 | 1.15 | (1.05,1.26) | 0.0028 | 1.36 | (1.12,1.65) | |
| Non-Diabetic | 918 | 361 | 39.3 | 936 | 414 | 44.2 | 1.10 | (0.99,1.22) | 0.0648 | 1.22 | (1.00,1.49) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0511 |
| <30 | 1028 | 408 | 39.7 | 1046 | 437 | 41.8 | 1.05 | (0.96,1.16) | 0.2833 | 1.11 | (0.92,1.34) | |
| >=30 | 884 | 366 | 41.4 | 919 | 468 | 50.9 | 1.21 | (1.10,1.33) | 0.0001 | 1.54 | (1.26,1.89) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.2497 |
| <130 | 793 | 335 | 42.2 | 819 | 367 | 44.8 | 1.08 | (0.97,1.19) | 0.1762 | 1.18 | (0.96,1.47) | |
| >=130 | 1119 | 439 | 39.2 | 1146 | 538 | 46.9 | 1.17 | (1.07,1.27) | 0.0008 | 1.37 | (1.15,1.65) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7502 |
| <75 | 901 | 372 | 41.3 | 896 | 412 | 46.0 | 1.10 | (1.00,1.21) | 0.0578 | 1.23 | (1.01,1.51) | |
| 75 to <85 | 622 | 251 | 40.4 | 674 | 307 | 45.5 | 1.14 | (1.01,1.28) | 0.0316 | 1.33 | (1.05,1.69) | |
| >=85 | 389 | 151 | 38.8 | 395 | 186 | 47.1 | 1.18 | (1.01,1.37) | 0.0370 | 1.39 | (1.01,1.89) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.2.1.2.1.2: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 5 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8705 |
| <30 | 150 | 61 | 40.7 | 138 | 70 | 50.7 | 1.20 | (0.95,1.51) | 0.1325 | 1.54 | (0.92,2.58) | |
| 30 to <45 | 530 | 202 | 38.1 | 541 | 238 | 44.0 | 1.12 | (0.97,1.28) | 0.1178 | 1.26 | (0.97,1.65) | |
| >=45 | 1231 | 511 | 41.5 | 1286 | 597 | 46.4 | 1.12 | (1.03,1.22) | 0.0062 | 1.27 | (1.07,1.51) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9365 |
| Normal (<30) | 738 | 296 | 40.1 | 761 | 345 | 45.3 | 1.12 | (1.00,1.25) | 0.0526 | 1.26 | (1.01,1.57) | |
| Microalbuminuria (30 to <=300) | 873 | 349 | 40.0 | 890 | 418 | 47.0 | 1.14 | (1.03,1.26) | 0.0104 | 1.34 | (1.09,1.65) | |
| Macroalbuminuria (>300) | 297 | 128 | 43.1 | 305 | 138 | 45.2 | 1.11 | (0.94,1.31) | 0.2326 | 1.23 | (0.86,1.76) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3805 |
| Low, moderate or high | 1413 | 573 | 40.6 | 1489 | 696 | 46.7 | 1.14 | (1.06,1.24) | 0.0007 | 1.33 | (1.13,1.56) | |
| Very high | 495 | 200 | 40.4 | 467 | 205 | 43.9 | 1.07 | (0.93,1.23) | 0.3725 | 1.17 | (0.88,1.55) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9673 |
| No | 389 | 151 | 38.8 | 388 | 169 | 43.6 | 1.13 | (0.96,1.33) | 0.1349 | 1.29 | (0.94,1.76) | |
| Yes | 1523 | 623 | 40.9 | 1577 | 736 | 46.7 | 1.13 | (1.04,1.21) | 0.0020 | 1.29 | (1.11,1.51) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5361 |
| No | 260 | 101 | 38.8 | 258 | 109 | 42.2 | 1.06 | (0.87,1.29) | 0.5392 | 1.18 | (0.80,1.73) | |
| Yes | 1652 | 673 | 40.7 | 1707 | 796 | 46.6 | 1.14 | (1.06,1.22) | 0.0006 | 1.31 | (1.13,1.52) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3881 |
| No | 218 | 84 | 38.5 | 237 | 109 | 46.0 | 1.22 | (1.00,1.50) | 0.0486 | 1.45 | (0.97,2.17) | |
| Yes | 1694 | 690 | 40.7 | 1728 | 796 | 46.1 | 1.11 | (1.04,1.20) | 0.0033 | 1.27 | (1.09,1.47) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**R.2.1.2.1.3**

R.2.1.2.1.3 KCCQ-OSS responder analysis (15 points)

Table R.2.1.2.1.3: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1912 | 283 | 14.8 | 1965 | 255 | 13.0 | 0.88 | (0.75,1.03) | 0.1033 | 0.86 | (0.71,1.03) | |
| Sex | | | | | | | | | | | | 0.8304 |
| Male | 1019 | 162 | 15.9 | 1047 | 143 | 13.7 | 0.87 | (0.71,1.06) | 0.1726 | 0.84 | (0.65,1.08) | |
| Female | 893 | 121 | 13.5 | 918 | 112 | 12.2 | 0.90 | (0.71,1.13) | 0.3644 | 0.88 | (0.66,1.17) | |
| Age [years] | | | | | | | | | | | | 0.5267 |
| <65 | 313 | 31 | 9.9 | 302 | 31 | 10.3 | 1.01 | (0.63,1.60) | 0.9751 | 1.01 | (0.59,1.72) | |
| >=65 | 1599 | 252 | 15.8 | 1663 | 224 | 13.5 | 0.86 | (0.73,1.01) | 0.0687 | 0.83 | (0.68,1.02) | |
| Region | | | | | | | | | | | | 0.1034 |
| North America | 264 | 42 | 15.9 | 260 | 36 | 13.8 | 0.84 | (0.56,1.26) | 0.3901 | 0.80 | (0.49,1.31) | |
| Latin America | 482 | 58 | 12.0 | 479 | 50 | 10.4 | 0.89 | (0.63,1.26) | 0.5019 | 0.87 | (0.58,1.31) | |
| Europe | 838 | 116 | 13.8 | 867 | 127 | 14.6 | 1.06 | (0.84,1.33) | 0.6383 | 1.07 | (0.81,1.41) | |
| Asia | 220 | 42 | 19.1 | 237 | 23 | 9.7 | 0.53 | (0.33,0.84) | 0.0072 | 0.46 | (0.27,0.81) | |
| Other | 108 | 25 | 23.1 | 122 | 19 | 15.6 | 0.72 | (0.43,1.21) | 0.2156 | 0.65 | (0.33,1.29) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.8066 |
| Diabetic | 994 | 143 | 14.4 | 1029 | 130 | 12.6 | 0.86 | (0.70,1.07) | 0.1836 | 0.84 | (0.65,1.09) | |
| Non-Diabetic | 918 | 140 | 15.3 | 936 | 125 | 13.4 | 0.90 | (0.72,1.12) | 0.3385 | 0.88 | (0.67,1.14) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9544 |
| <30 | 1028 | 151 | 14.7 | 1046 | 136 | 13.0 | 0.88 | (0.72,1.09) | 0.2543 | 0.86 | (0.67,1.11) | |
| >=30 | 884 | 132 | 14.9 | 919 | 119 | 12.9 | 0.88 | (0.70,1.10) | 0.2515 | 0.85 | (0.65,1.12) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.2998 |
| <130 | 793 | 103 | 13.0 | 819 | 106 | 12.9 | 0.98 | (0.76,1.25) | 0.8520 | 0.97 | (0.72,1.31) | |
| >=130 | 1119 | 180 | 16.1 | 1146 | 149 | 13.0 | 0.83 | (0.68,1.00) | 0.0548 | 0.79 | (0.62,1.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3032 |
| <75 | 901 | 126 | 14.0 | 896 | 126 | 14.1 | 1.00 | (0.80,1.25) | 0.9899 | 1.00 | (0.76,1.32) | |
| 75 to <85 | 622 | 94 | 15.1 | 674 | 80 | 11.9 | 0.77 | (0.59,1.01) | 0.0598 | 0.73 | (0.53,1.01) | |
| >=85 | 389 | 63 | 16.2 | 395 | 49 | 12.4 | 0.82 | (0.58,1.15) | 0.2435 | 0.78 | (0.51,1.17) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.2.1.2.1.3: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2193 |
| <30 | 150 | 31 | 20.7 | 138 | 16 | 11.6 | 0.59 | (0.35,1.02) | 0.0605 | 0.51 | (0.26,1.01) | |
| 30 to <45 | 530 | 92 | 17.4 | 541 | 75 | 13.9 | 0.82 | (0.62,1.08) | 0.1590 | 0.79 | (0.56,1.10) | |
| >=45 | 1231 | 160 | 13.0 | 1286 | 164 | 12.8 | 0.97 | (0.79,1.18) | 0.7299 | 0.96 | (0.76,1.22) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.6143 |
| Normal (<30) | 738 | 111 | 15.0 | 761 | 99 | 13.0 | 0.87 | (0.68,1.11) | 0.2592 | 0.84 | (0.62,1.13) | |
| Microalbuminuria (30 to <=300) | 873 | 124 | 14.2 | 890 | 115 | 12.9 | 0.93 | (0.74,1.17) | 0.5334 | 0.92 | (0.69,1.21) | |
| Macroalbuminuria (>300) | 297 | 48 | 16.2 | 305 | 38 | 12.5 | 0.74 | (0.51,1.08) | 0.1228 | 0.69 | (0.43,1.11) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0267 |
| Low, moderate or high | 1413 | 186 | 13.2 | 1489 | 192 | 12.9 | 0.98 | (0.81,1.18) | 0.8067 | 0.97 | (0.78,1.21) | |
| Very high | 495 | 97 | 19.6 | 467 | 60 | 12.8 | 0.66 | (0.50,0.88) | 0.0051 | 0.60 | (0.42,0.86) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.0683 |
| No | 389 | 73 | 18.8 | 388 | 50 | 12.9 | 0.68 | (0.49,0.93) | 0.0168 | 0.61 | (0.41,0.92) | |
| Yes | 1523 | 210 | 13.8 | 1577 | 205 | 13.0 | 0.95 | (0.80,1.13) | 0.5733 | 0.94 | (0.76,1.16) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.1185 |
| No | 260 | 52 | 20.0 | 258 | 36 | 14.0 | 0.67 | (0.46,0.97) | 0.0355 | 0.61 | (0.38,0.98) | |
| Yes | 1652 | 231 | 14.0 | 1707 | 219 | 12.8 | 0.93 | (0.78,1.10) | 0.3833 | 0.91 | (0.75,1.12) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9025 |
| No | 218 | 32 | 14.7 | 237 | 32 | 13.5 | 0.90 | (0.57,1.42) | 0.6645 | 0.89 | (0.52,1.52) | |
| Yes | 1694 | 251 | 14.8 | 1728 | 223 | 12.9 | 0.88 | (0.74,1.03) | 0.1183 | 0.85 | (0.70,1.04) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.2.1.2.1.3: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1912 | 407 | 21.3 | 1965 | 446 | 22.7 | 1.03 | (0.92,1.15) | 0.5600 | 1.07 | (0.90,1.27) | |
| Sex | | | | | | | | | | | | 0.9096 |
| Male | 1019 | 193 | 18.9 | 1047 | 207 | 19.8 | 1.04 | (0.89,1.22) | 0.6289 | 1.05 | (0.82,1.34) | |
| Female | 893 | 214 | 24.0 | 918 | 239 | 26.0 | 1.03 | (0.88,1.20) | 0.7279 | 1.08 | (0.85,1.38) | |
| Age [years] | | | | | | | | | | | | 0.5402 |
| <65 | 313 | 84 | 26.8 | 302 | 91 | 30.1 | 1.10 | (0.87,1.40) | 0.4152 | 1.26 | (0.84,1.89) | |
| >=65 | 1599 | 323 | 20.2 | 1663 | 355 | 21.3 | 1.01 | (0.90,1.15) | 0.8157 | 1.03 | (0.85,1.24) | |
| Region | | | | | | | | | | | | 0.1888 |
| North America | 264 | 51 | 19.3 | 260 | 48 | 18.5 | 1.06 | (0.76,1.47) | 0.7477 | 1.08 | (0.66,1.75) | |
| Latin America | 482 | 146 | 30.3 | 479 | 169 | 35.3 | 1.12 | (0.94,1.33) | 0.1961 | 1.29 | (0.94,1.76) | |
| Europe | 838 | 156 | 18.6 | 867 | 148 | 17.1 | 0.89 | (0.73,1.07) | 0.2174 | 0.85 | (0.65,1.11) | |
| Asia | 220 | 28 | 12.7 | 237 | 47 | 19.8 | 1.44 | (0.96,2.16) | 0.0751 | 1.63 | (0.94,2.81) | |
| Other | 108 | 26 | 24.1 | 122 | 34 | 27.9 | 0.95 | (0.64,1.40) | 0.7918 | 0.95 | (0.49,1.86) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2058 |
| Diabetic | 994 | 217 | 21.8 | 1029 | 249 | 24.2 | 1.10 | (0.95,1.28) | 0.2065 | 1.18 | (0.93,1.49) | |
| Non-Diabetic | 918 | 190 | 20.7 | 936 | 197 | 21.0 | 0.96 | (0.81,1.12) | 0.5858 | 0.95 | (0.74,1.23) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1686 |
| <30 | 1028 | 210 | 20.4 | 1046 | 206 | 19.7 | 0.96 | (0.81,1.12) | 0.5771 | 0.92 | (0.73,1.18) | |
| >=30 | 884 | 197 | 22.3 | 919 | 240 | 26.1 | 1.12 | (0.96,1.30) | 0.1623 | 1.24 | (0.97,1.59) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1384 |
| <130 | 793 | 184 | 23.2 | 819 | 178 | 21.7 | 0.94 | (0.79,1.11) | 0.4607 | 0.93 | (0.71,1.20) | |
| >=130 | 1119 | 223 | 19.9 | 1146 | 268 | 23.4 | 1.11 | (0.96,1.29) | 0.1590 | 1.19 | (0.95,1.49) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5934 |
| <75 | 901 | 191 | 21.2 | 896 | 192 | 21.4 | 0.97 | (0.82,1.14) | 0.7200 | 0.95 | (0.74,1.23) | |
| 75 to <85 | 622 | 128 | 20.6 | 674 | 152 | 22.6 | 1.09 | (0.90,1.33) | 0.3713 | 1.18 | (0.88,1.60) | |
| >=85 | 389 | 88 | 22.6 | 395 | 102 | 25.8 | 1.08 | (0.86,1.37) | 0.5010 | 1.16 | (0.80,1.69) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.2.1.2.1.3: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2529 |
| <30 | 150 | 36 | 24.0 | 138 | 42 | 30.4 | 1.14 | (0.80,1.64) | 0.4623 | 1.40 | (0.77,2.54) | |
| 30 to <45 | 530 | 98 | 18.5 | 541 | 128 | 23.7 | 1.19 | (0.95,1.48) | 0.1324 | 1.33 | (0.95,1.85) | |
| >=45 | 1231 | 273 | 22.2 | 1286 | 276 | 21.5 | 0.96 | (0.84,1.11) | 0.6056 | 0.94 | (0.76,1.17) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.5140 |
| Normal (<30) | 738 | 144 | 19.5 | 761 | 165 | 21.7 | 1.08 | (0.90,1.29) | 0.4262 | 1.13 | (0.85,1.49) | |
| Microalbuminuria (30 to <=300) | 873 | 195 | 22.3 | 890 | 207 | 23.3 | 0.97 | (0.82,1.14) | 0.6752 | 0.97 | (0.76,1.25) | |
| Macroalbuminuria (>300) | 297 | 67 | 22.6 | 305 | 72 | 23.6 | 1.14 | (0.87,1.49) | 0.3544 | 1.23 | (0.79,1.91) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4841 |
| Low, moderate or high | 1413 | 307 | 21.7 | 1489 | 334 | 22.4 | 1.01 | (0.89,1.14) | 0.8887 | 1.01 | (0.83,1.23) | |
| Very high | 495 | 99 | 20.0 | 467 | 110 | 23.6 | 1.11 | (0.88,1.40) | 0.3830 | 1.24 | (0.88,1.76) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6229 |
| No | 389 | 80 | 20.6 | 388 | 87 | 22.4 | 1.09 | (0.84,1.42) | 0.4976 | 1.17 | (0.80,1.72) | |
| Yes | 1523 | 327 | 21.5 | 1577 | 359 | 22.8 | 1.02 | (0.90,1.15) | 0.7719 | 1.04 | (0.86,1.26) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.2099 |
| No | 260 | 53 | 20.4 | 258 | 48 | 18.6 | 0.85 | (0.61,1.18) | 0.3286 | 0.82 | (0.50,1.34) | |
| Yes | 1652 | 354 | 21.4 | 1707 | 398 | 23.3 | 1.06 | (0.94,1.19) | 0.3253 | 1.11 | (0.92,1.33) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.6829 |
| No | 218 | 41 | 18.8 | 237 | 45 | 19.0 | 1.11 | (0.79,1.55) | 0.5618 | 1.10 | (0.65,1.86) | |
| Yes | 1694 | 366 | 21.6 | 1728 | 401 | 23.2 | 1.03 | (0.91,1.15) | 0.6670 | 1.06 | (0.89,1.27) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**R.2.2**

**R.2.2.1**

R.2.2.1 Adverse events overall

Table R.2.2.1: 1 Proportion of patients with any adverse event occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 1800 | 90.0 | 2052 | 1833 | 89.3 | 0.5122 | 0.99 | ( 0.97, 1.01) | 0.93 | (0.76,1.14) | -0.01 | (-0.03,0.01) | |
| Sex | | | | | | | | | | | | | | 0.8169 |
| Male | 1065 | 954 | 89.6 | 1093 | 970 | 88.7 | 0.5348 | 0.99 | ( 0.96, 1.02) | 0.92 | (0.70,1.20) | -0.01 | (-0.03,0.02) | |
| Female | 936 | 846 | 90.4 | 959 | 863 | 90.0 | 0.7726 | 1.00 | ( 0.97, 1.03) | 0.96 | (0.71,1.29) | 0.00 | (-0.03,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.6849 |
| <65 | 331 | 297 | 89.7 | 313 | 276 | 88.2 | 0.5304 | 0.98 | ( 0.93, 1.04) | 0.85 | (0.52,1.40) | -0.02 | (-0.06,0.03) | |
| >=65 | 1670 | 1503 | 90.0 | 1739 | 1557 | 89.5 | 0.6538 | 0.99 | ( 0.97, 1.02) | 0.95 | (0.76,1.19) | 0.00 | (-0.03,0.02) | |
| Region | | | | | | | | | | | | | | 0.8072 |
| North America | 273 | 262 | 96.0 | 273 | 263 | 96.3 | 0.8239 | 1.00 | ( 0.97, 1.04) | 1.10 | (0.46,2.64) | 0.00 | (-0.03,0.04) | |
| Latin America | 511 | 456 | 89.2 | 504 | 450 | 89.3 | 0.9799 | 1.00 | ( 0.96, 1.04) | 1.01 | (0.68,1.50) | 0.00 | (-0.04,0.04) | |
| Europe | 865 | 754 | 87.2 | 894 | 765 | 85.6 | 0.3293 | 0.98 | ( 0.95, 1.02) | 0.87 | (0.66,1.15) | -0.02 | (-0.05,0.02) | |
| Asia | 231 | 219 | 94.8 | 248 | 232 | 93.5 | 0.5580 | 0.99 | ( 0.94, 1.03) | 0.79 | (0.37,1.72) | -0.01 | (-0.05,0.03) | |
| Other | 121 | 109 | 90.1 | 133 | 123 | 92.5 | 0.4973 | 1.03 | ( 0.95, 1.11) | 1.35 | (0.56,3.26) | 0.02 | (-0.05,0.09) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3404 |
| Diabetic | 1045 | 943 | 90.2 | 1081 | 978 | 90.5 | 0.8559 | 1.00 | ( 0.98, 1.03) | 1.03 | (0.77,1.37) | 0.00 | (-0.02,0.03) | |
| Non-Diabetic | 956 | 857 | 89.6 | 971 | 855 | 88.1 | 0.2674 | 0.98 | ( 0.95, 1.01) | 0.85 | (0.64,1.13) | -0.02 | (-0.04,0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3840 |
| <30 | 1086 | 982 | 90.4 | 1094 | 991 | 90.6 | 0.8977 | 1.00 | ( 0.97, 1.03) | 1.02 | (0.77,1.36) | 0.00 | (-0.02,0.03) | |
| >=30 | 915 | 818 | 89.4 | 958 | 842 | 87.9 | 0.3043 | 0.98 | ( 0.95, 1.02) | 0.86 | (0.65,1.15) | -0.02 | (-0.04,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1753 |
| <130 | 827 | 745 | 90.1 | 853 | 776 | 91.0 | 0.5340 | 1.01 | ( 0.98, 1.04) | 1.11 | (0.80,1.54) | 0.01 | (-0.02,0.04) | |
| >=130 | 1174 | 1055 | 89.9 | 1199 | 1057 | 88.2 | 0.1839 | 0.98 | ( 0.95, 1.01) | 0.84 | (0.65,1.09) | -0.02 | (-0.04,0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0065 |
| <75 | 935 | 838 | 89.6 | 934 | 862 | 92.3 | 0.0445 | 1.03 | (>1.00, 1.06) | 1.39 | (1.01,1.91) | 0.03 | ( 0.00,0.05) | |
| 75 to <85 | 657 | 588 | 89.5 | 703 | 603 | 85.8 | 0.0376 | 0.96 | ( 0.92,<1.00) | 0.71 | (0.51,0.98) | -0.04 | (-0.07,0.00) | |
| >=85 | 409 | 374 | 91.4 | 415 | 368 | 88.7 | 0.1845 | 0.97 | ( 0.93, 1.01) | 0.73 | (0.46,1.16) | -0.03 | (-0.07,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 1 Proportion of patients with any adverse event occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0290 |
| <30 | 161 | 150 | 93.2 | 148 | 141 | 95.3 | 0.4305 | 1.02 ( 0.97, 1.08) | 1.48 (0.56,3.92) | 0.02 (-0.03,0.07) | |
| 30 to <45 | 550 | 491 | 89.3 | 564 | 520 | 92.2 | 0.0919 | 1.03 ( 0.99, 1.07) | 1.42 (0.94,2.14) | 0.03 ( 0.00,0.06) | |
| >=45 | 1289 | 1158 | 89.8 | 1340 | 1172 | 87.5 | 0.0552 | 0.97 ( 0.95,>1.00) | 0.79 (0.62,1.01) | -0.02 (-0.05,0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.9436 |
| Normal (<30) | 764 | 674 | 88.2 | 787 | 693 | 88.1 | 0.9205 | 1.00 ( 0.96, 1.04) | 0.98 (0.72,1.34) | 0.00 (-0.03,0.03) | |
| Microalbuminuria (30 to <=300) | 921 | 828 | 89.9 | 938 | 835 | 89.0 | 0.5353 | 0.99 ( 0.96, 1.02) | 0.91 (0.68,1.22) | -0.01 (-0.04,0.02) | |
| Macroalbuminuria (>300) | 311 | 294 | 94.5 | 318 | 298 | 93.7 | 0.6609 | 0.99 ( 0.95, 1.03) | 0.86 (0.44,1.68) | -0.01 (-0.04,0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0240 |
| Low, moderate or high | 1477 | 1314 | 89.0 | 1548 | 1353 | 87.4 | 0.1840 | 0.98 ( 0.96, 1.01) | 0.86 (0.69,1.07) | -0.02 (-0.04,0.01) | |
| Very high | 519 | 482 | 92.9 | 495 | 473 | 95.6 | 0.0679 | 1.03 (<1.00, 1.06) | 1.65 (0.96,2.84) | 0.03 ( 0.00,0.06) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.4558 |
| No | 411 | 379 | 92.2 | 410 | 370 | 90.2 | 0.3183 | 0.98 ( 0.94, 1.02) | 0.78 (0.48,1.27) | -0.02 (-0.06,0.02) | |
| Yes | 1590 | 1421 | 89.4 | 1642 | 1463 | 89.1 | 0.8028 | 1.00 ( 0.97, 1.02) | 0.97 (0.78,1.21) | 0.00 (-0.02,0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.7898 |
| No | 282 | 258 | 91.5 | 277 | 250 | 90.3 | 0.6117 | 0.99 ( 0.94, 1.04) | 0.86 (0.48,1.53) | -0.01 (-0.06,0.04) | |
| Yes | 1719 | 1542 | 89.7 | 1775 | 1583 | 89.2 | 0.6169 | 0.99 ( 0.97, 1.02) | 0.95 (0.76,1.17) | -0.01 (-0.03,0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9702 |
| No | 229 | 205 | 89.5 | 250 | 222 | 88.8 | 0.8003 | 0.99 ( 0.93, 1.06) | 0.93 (0.52,1.65) | -0.01 (-0.06,0.05) | |
| Yes | 1772 | 1595 | 90.0 | 1802 | 1611 | 89.4 | 0.5481 | 0.99 ( 0.97, 1.02) | 0.94 (0.75,1.16) | -0.01 (-0.03,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 1749 | 87.4 | 2052 | 1790 | 87.2 | 0.8676 | 1.00 | ( 0.97, 1.02) | 0.98 | (0.82,1.18) | 0.00 | (-0.02,0.02) | |
| Sex | | | | | | | | | | | | | | 0.6618 |
| Male | 1065 | 921 | 86.5 | 1093 | 948 | 86.7 | 0.8620 | 1.00 | ( 0.97, 1.04) | 1.02 | (0.80,1.31) | 0.00 | (-0.03,0.03) | |
| Female | 936 | 828 | 88.5 | 959 | 842 | 87.8 | 0.6561 | 0.99 | ( 0.96, 1.03) | 0.94 | (0.71,1.24) | -0.01 | (-0.04,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.6267 |
| <65 | 331 | 287 | 86.7 | 313 | 267 | 85.3 | 0.6077 | 0.98 | ( 0.92, 1.05) | 0.89 | (0.57,1.39) | -0.01 | (-0.07,0.04) | |
| >=65 | 1670 | 1462 | 87.5 | 1739 | 1523 | 87.6 | 0.9759 | 1.00 | ( 0.98, 1.03) | 1.00 | (0.82,1.23) | 0.00 | (-0.02,0.02) | |
| Region | | | | | | | | | | | | | | 0.8436 |
| North America | 273 | 259 | 94.9 | 273 | 257 | 94.1 | 0.7072 | 0.99 | ( 0.95, 1.03) | 0.87 | (0.42,1.82) | -0.01 | (-0.05,0.03) | |
| Latin America | 511 | 437 | 85.5 | 504 | 435 | 86.3 | 0.7173 | 1.01 | ( 0.96, 1.06) | 1.07 | (0.75,1.52) | 0.01 | (-0.03,0.05) | |
| Europe | 865 | 729 | 84.3 | 894 | 745 | 83.3 | 0.5911 | 0.99 | ( 0.95, 1.03) | 0.93 | (0.72,1.20) | -0.01 | (-0.04,0.02) | |
| Asia | 231 | 216 | 93.5 | 248 | 230 | 92.7 | 0.7413 | 0.99 | ( 0.94, 1.04) | 0.89 | (0.44,1.80) | -0.01 | (-0.05,0.04) | |
| Other | 121 | 108 | 89.3 | 133 | 123 | 92.5 | 0.3710 | 1.04 | ( 0.96, 1.12) | 1.48 | (0.62,3.51) | 0.03 | (-0.04,0.10) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2485 |
| Diabetic | 1045 | 915 | 87.6 | 1081 | 957 | 88.5 | 0.4909 | 1.01 | ( 0.98, 1.04) | 1.10 | (0.84,1.43) | 0.01 | (-0.02,0.04) | |
| Non-Diabetic | 956 | 834 | 87.2 | 971 | 833 | 85.8 | 0.3514 | 0.98 | ( 0.95, 1.02) | 0.88 | (0.68,1.15) | -0.01 | (-0.04,0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4154 |
| <30 | 1086 | 955 | 87.9 | 1094 | 969 | 88.6 | 0.6443 | 1.01 | ( 0.98, 1.04) | 1.06 | (0.82,1.38) | 0.01 | (-0.02,0.03) | |
| >=30 | 915 | 794 | 86.8 | 958 | 821 | 85.7 | 0.4992 | 0.99 | ( 0.95, 1.02) | 0.91 | (0.70,1.19) | -0.01 | (-0.04,0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5870 |
| <130 | 827 | 725 | 87.7 | 853 | 752 | 88.2 | 0.7565 | 1.01 | ( 0.97, 1.04) | 1.05 | (0.78,1.40) | 0.00 | (-0.03,0.04) | |
| >=130 | 1174 | 1024 | 87.2 | 1199 | 1038 | 86.6 | 0.6385 | 0.99 | ( 0.96, 1.02) | 0.94 | (0.74,1.20) | -0.01 | (-0.03,0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0197 |
| <75 | 935 | 816 | 87.3 | 934 | 843 | 90.3 | 0.0411 | 1.03 | (>1.00, 1.07) | 1.35 | (1.01,1.80) | 0.03 | ( 0.00,0.06) | |
| 75 to <85 | 657 | 571 | 86.9 | 703 | 587 | 83.5 | 0.0771 | 0.96 | ( 0.92,>1.00) | 0.76 | (0.56,1.03) | -0.03 | (-0.07,0.00) | |
| >=85 | 409 | 362 | 88.5 | 415 | 360 | 86.7 | 0.4427 | 0.98 | ( 0.93, 1.03) | 0.85 | (0.56,1.29) | -0.02 | (-0.06,0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0255 |
| <30 | 161 | 144 | 89.4 | 148 | 138 | 93.2 | 0.2371 | 1.04 ( 0.97, 1.12) | 1.63 (0.72,3.68) | 0.04 (-0.02,0.10) | |
| 30 to <45 | 550 | 481 | 87.5 | 564 | 513 | 91.0 | 0.0594 | 1.04 (<1.00, 1.08) | 1.44 (0.98,2.12) | 0.04 ( 0.00,0.07) | |
| >=45 | 1289 | 1123 | 87.1 | 1340 | 1139 | 85.0 | 0.1166 | 0.98 ( 0.95, 1.01) | 0.84 (0.67,1.05) | -0.02 (-0.05,0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.8865 |
| Normal (<30) | 764 | 663 | 86.8 | 787 | 677 | 86.0 | 0.6636 | 0.99 ( 0.95, 1.03) | 0.94 (0.70,1.25) | -0.01 (-0.04,0.03) | |
| Microalbuminuria (30 to <=300) | 921 | 798 | 86.6 | 938 | 814 | 86.8 | 0.9315 | 1.00 ( 0.97, 1.04) | 1.01 (0.77,1.32) | 0.00 (-0.03,0.03) | |
| Macroalbuminuria (>300) | 311 | 284 | 91.3 | 318 | 292 | 91.8 | 0.8195 | 1.01 ( 0.96, 1.05) | 1.07 (0.61,1.87) | 0.01 (-0.04,0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0329 |
| Low, moderate or high | 1477 | 1276 | 86.4 | 1548 | 1319 | 85.2 | 0.3510 | 0.99 ( 0.96, 1.02) | 0.91 (0.74,1.11) | -0.01 (-0.04,0.01) | |
| Very high | 519 | 469 | 90.4 | 495 | 464 | 93.7 | 0.0478 | 1.04 (>1.00, 1.08) | 1.60 (1.00,2.54) | 0.03 ( 0.00,0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.5902 |
| No | 411 | 367 | 89.3 | 410 | 361 | 88.0 | 0.5734 | 0.99 ( 0.94, 1.04) | 0.88 (0.57,1.36) | -0.01 (-0.06,0.03) | |
| Yes | 1590 | 1382 | 86.9 | 1642 | 1429 | 87.0 | 0.9261 | 1.00 ( 0.97, 1.03) | 1.01 (0.82,1.24) | 0.00 (-0.02,0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.8755 |
| No | 282 | 249 | 88.3 | 277 | 243 | 87.7 | 0.8350 | 0.99 ( 0.93, 1.06) | 0.95 (0.57,1.58) | -0.01 (-0.06,0.05) | |
| Yes | 1719 | 1500 | 87.3 | 1775 | 1547 | 87.2 | 0.9259 | 1.00 ( 0.97, 1.02) | 0.99 (0.81,1.21) | 0.00 (-0.02,0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9895 |
| No | 229 | 200 | 87.3 | 250 | 218 | 87.2 | 0.9644 | 1.00 ( 0.93, 1.07) | 0.99 (0.58,1.69) | 0.00 (-0.06,0.06) | |
| Yes | 1772 | 1549 | 87.4 | 1802 | 1572 | 87.2 | 0.8723 | 1.00 ( 0.97, 1.02) | 0.98 (0.81,1.20) | 0.00 (-0.02,0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 3 Proportion of patients with serious adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 1210 | 60.5 | 2052 | 1171 | 57.1 | 0.0278 | 0.94 | (0.90, 0.99) | 0.87 | (0.77,0.98) | -0.03 | (-0.06, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.6639 |
| Male | 1065 | 676 | 63.5 | 1093 | 648 | 59.3 | 0.0458 | 0.93 | (0.87,<1.00) | 0.84 | (0.70,1.00) | -0.04 | (-0.08, 0.00) | |
| Female | 936 | 534 | 57.1 | 959 | 523 | 54.5 | 0.2703 | 0.96 | (0.88, 1.04) | 0.90 | (0.75,1.08) | -0.03 | (-0.07, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.4721 |
| <65 | 331 | 183 | 55.3 | 313 | 171 | 54.6 | 0.8675 | 0.99 | (0.86, 1.14) | 0.97 | (0.71,1.33) | -0.01 | (-0.08, 0.07) | |
| >=65 | 1670 | 1027 | 61.5 | 1739 | 1000 | 57.5 | 0.0176 | 0.94 | (0.88, 0.99) | 0.85 | (0.74,0.97) | -0.04 | (-0.07,-0.01) | |
| Region | | | | | | | | | | | | | | 0.8833 |
| North America | 273 | 191 | 70.0 | 273 | 189 | 69.2 | 0.8524 | 0.99 | (0.89, 1.11) | 0.97 | (0.67,1.39) | -0.01 | (-0.08, 0.07) | |
| Latin America | 511 | 304 | 59.5 | 504 | 287 | 56.9 | 0.4108 | 0.96 | (0.86, 1.06) | 0.90 | (0.70,1.16) | -0.03 | (-0.09, 0.04) | |
| Europe | 865 | 497 | 57.5 | 894 | 474 | 53.0 | 0.0614 | 0.92 | (0.85,>1.00) | 0.84 | (0.69,1.01) | -0.04 | (-0.09, 0.00) | |
| Asia | 231 | 141 | 61.0 | 248 | 144 | 58.1 | 0.5076 | 0.95 | (0.82, 1.10) | 0.88 | (0.61,1.27) | -0.03 | (-0.12, 0.06) | |
| Other | 121 | 77 | 63.6 | 133 | 77 | 57.9 | 0.3496 | 0.91 | (0.75, 1.11) | 0.79 | (0.47,1.30) | -0.06 | (-0.18, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7354 |
| Diabetic | 1045 | 655 | 62.7 | 1081 | 634 | 58.6 | 0.0573 | 0.94 | (0.87,>1.00) | 0.84 | (0.71,1.01) | -0.04 | (-0.08, 0.00) | |
| Non-Diabetic | 956 | 555 | 58.1 | 971 | 537 | 55.3 | 0.2231 | 0.95 | (0.88, 1.03) | 0.89 | (0.75,1.07) | -0.03 | (-0.07, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0164 |
| <30 | 1086 | 678 | 62.4 | 1094 | 608 | 55.6 | 0.0011 | 0.89 | (0.83, 0.95) | 0.75 | (0.63,0.89) | -0.07 | (-0.11,-0.03) | |
| >=30 | 915 | 532 | 58.1 | 958 | 563 | 58.8 | 0.7834 | 1.01 | (0.94, 1.09) | 1.03 | (0.85,1.23) | 0.01 | (-0.04, 0.05) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7192 |
| <130 | 827 | 505 | 61.1 | 853 | 497 | 58.3 | 0.2424 | 0.95 | (0.88, 1.03) | 0.89 | (0.73,1.08) | -0.03 | (-0.07, 0.02) | |
| >=130 | 1174 | 705 | 60.1 | 1199 | 674 | 56.2 | 0.0582 | 0.94 | (0.87,>1.00) | 0.85 | (0.73,1.01) | -0.04 | (-0.08, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6218 |
| <75 | 935 | 581 | 62.1 | 934 | 563 | 60.3 | 0.4091 | 0.97 | (0.90, 1.04) | 0.92 | (0.77,1.11) | -0.02 | (-0.06, 0.03) | |
| 75 to <85 | 657 | 383 | 58.3 | 703 | 379 | 53.9 | 0.1036 | 0.92 | (0.84, 1.02) | 0.84 | (0.68,1.04) | -0.04 | (-0.10, 0.01) | |
| >=85 | 409 | 246 | 60.1 | 415 | 229 | 55.2 | 0.1492 | 0.92 | (0.82, 1.03) | 0.82 | (0.62,1.08) | -0.05 | (-0.12, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 3 Proportion of patients with serious adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9522 |
| <30 | 161 | 121 | 75.2 | 148 | 106 | 71.6 | 0.4822 | 0.95 | (0.83, 1.09) | 0.83 | (0.50,1.38) | -0.04 | (-0.13, 0.06) | |
| 30 to <45 | 550 | 359 | 65.3 | 564 | 344 | 61.0 | 0.1388 | 0.93 | (0.85, 1.02) | 0.83 | (0.65,1.06) | -0.04 | (-0.10, 0.01) | |
| >=45 | 1289 | 730 | 56.6 | 1340 | 721 | 53.8 | 0.1451 | 0.95 | (0.89, 1.02) | 0.89 | (0.76,1.04) | -0.03 | (-0.07, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7905 |
| Normal (<30) | 764 | 423 | 55.4 | 787 | 419 | 53.2 | 0.4007 | 0.96 | (0.88, 1.05) | 0.92 | (0.75,1.12) | -0.02 | (-0.07, 0.03) | |
| Microalbuminuria (30 to <=300) | 921 | 569 | 61.8 | 938 | 548 | 58.4 | 0.1393 | 0.95 | (0.88, 1.02) | 0.87 | (0.72,1.05) | -0.03 | (-0.08, 0.01) | |
| Macroalbuminuria (>300) | 311 | 216 | 69.5 | 318 | 202 | 63.5 | 0.1152 | 0.91 | (0.82, 1.02) | 0.77 | (0.55,1.07) | -0.06 | (-0.13, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8262 |
| Low, moderate or high | 1477 | 839 | 56.8 | 1548 | 837 | 54.1 | 0.1304 | 0.95 | (0.89, 1.01) | 0.90 | (0.78,1.03) | -0.03 | (-0.06, 0.01) | |
| Very high | 519 | 370 | 71.3 | 495 | 332 | 67.1 | 0.1455 | 0.94 | (0.87, 1.02) | 0.82 | (0.63,1.07) | -0.04 | (-0.10, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9216 |
| No | 411 | 273 | 66.4 | 410 | 256 | 62.4 | 0.2331 | 0.94 | (0.85, 1.04) | 0.84 | (0.63,1.12) | -0.04 | (-0.11, 0.03) | |
| Yes | 1590 | 937 | 58.9 | 1642 | 915 | 55.7 | 0.0654 | 0.95 | (0.89,>1.00) | 0.88 | (0.76,1.01) | -0.03 | (-0.07, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4950 |
| No | 282 | 177 | 62.8 | 277 | 157 | 56.7 | 0.1423 | 0.90 | (0.79, 1.04) | 0.78 | (0.55,1.09) | -0.06 | (-0.14, 0.02) | |
| Yes | 1719 | 1033 | 60.1 | 1775 | 1014 | 57.1 | 0.0751 | 0.95 | (0.90, 1.01) | 0.88 | (0.77,1.01) | -0.03 | (-0.06, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4427 |
| No | 229 | 128 | 55.9 | 250 | 124 | 49.6 | 0.1681 | 0.89 | (0.75, 1.05) | 0.78 | (0.54,1.11) | -0.06 | (-0.15, 0.03) | |
| Yes | 1772 | 1082 | 61.1 | 1802 | 1047 | 58.1 | 0.0715 | 0.95 | (0.90,>1.00) | 0.88 | (0.77,1.01) | -0.03 | (-0.06, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 987 | 49.3 | 2052 | 957 | 46.6 | 0.0868 | 0.95 | (0.89, 1.01) | 0.90 | (0.79,1.02) | -0.03 | (-0.06, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.8803 |
| Male | 1065 | 551 | 51.7 | 1093 | 537 | 49.1 | 0.2260 | 0.95 | (0.87, 1.03) | 0.90 | (0.76,1.07) | -0.03 | (-0.07, 0.02) | |
| Female | 936 | 436 | 46.6 | 959 | 420 | 43.8 | 0.2231 | 0.94 | (0.85, 1.04) | 0.89 | (0.75,1.07) | -0.03 | (-0.07, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.3119 |
| <65 | 331 | 140 | 42.3 | 313 | 136 | 43.5 | 0.7673 | 1.03 | (0.86, 1.23) | 1.05 | (0.77,1.43) | 0.01 | (-0.06, 0.09) | |
| >=65 | 1670 | 847 | 50.7 | 1739 | 821 | 47.2 | 0.0406 | 0.93 | (0.87,<1.00) | 0.87 | (0.76,0.99) | -0.04 | (-0.07, 0.00) | |
| Region | | | | | | | | | | | | | | 0.9460 |
| North America | 273 | 173 | 63.4 | 273 | 166 | 60.8 | 0.5369 | 0.96 | (0.84, 1.09) | 0.90 | (0.63,1.27) | -0.03 | (-0.11, 0.06) | |
| Latin America | 511 | 235 | 46.0 | 504 | 223 | 44.2 | 0.5770 | 0.96 | (0.84, 1.10) | 0.93 | (0.73,1.19) | -0.02 | (-0.08, 0.04) | |
| Europe | 865 | 408 | 47.2 | 894 | 388 | 43.4 | 0.1125 | 0.92 | (0.83, 1.02) | 0.86 | (0.71,1.04) | -0.04 | (-0.08, 0.01) | |
| Asia | 231 | 109 | 47.2 | 248 | 117 | 47.2 | 0.9985 | 1.00 | (0.83, 1.21) | 1.00 | (0.70,1.43) | 0.00 | (-0.09, 0.09) | |
| Other | 121 | 62 | 51.2 | 133 | 63 | 47.4 | 0.5377 | 0.92 | (0.72, 1.19) | 0.86 | (0.52,1.40) | -0.04 | (-0.16, 0.08) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9844 |
| Diabetic | 1045 | 528 | 50.5 | 1081 | 516 | 47.7 | 0.1978 | 0.94 | (0.87, 1.03) | 0.89 | (0.75,1.06) | -0.03 | (-0.07, 0.01) | |
| Non-Diabetic | 956 | 459 | 48.0 | 971 | 441 | 45.4 | 0.2535 | 0.95 | (0.86, 1.04) | 0.90 | (0.75,1.08) | -0.03 | (-0.07, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0623 |
| <30 | 1086 | 549 | 50.6 | 1094 | 494 | 45.2 | 0.0117 | 0.89 | (0.82, 0.98) | 0.81 | (0.68,0.95) | -0.05 | (-0.10,-0.01) | |
| >=30 | 915 | 438 | 47.9 | 958 | 463 | 48.3 | 0.8418 | 1.01 | (0.92, 1.11) | 1.02 | (0.85,1.22) | 0.00 | (-0.04, 0.05) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9672 |
| <130 | 827 | 417 | 50.4 | 853 | 406 | 47.6 | 0.2466 | 0.94 | (0.86, 1.04) | 0.89 | (0.74,1.08) | -0.03 | (-0.08, 0.02) | |
| >=130 | 1174 | 570 | 48.6 | 1199 | 551 | 46.0 | 0.2052 | 0.95 | (0.87, 1.03) | 0.90 | (0.77,1.06) | -0.03 | (-0.07, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3075 |
| <75 | 935 | 473 | 50.6 | 934 | 468 | 50.1 | 0.8352 | 0.99 | (0.91, 1.08) | 0.98 | (0.82,1.18) | 0.00 | (-0.05, 0.04) | |
| 75 to <85 | 657 | 314 | 47.8 | 703 | 313 | 44.5 | 0.2268 | 0.93 | (0.83, 1.04) | 0.88 | (0.71,1.09) | -0.03 | (-0.09, 0.02) | |
| >=85 | 409 | 200 | 48.9 | 415 | 176 | 42.4 | 0.0615 | 0.87 | (0.75, 1.01) | 0.77 | (0.58,1.01) | -0.06 | (-0.13, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2108 |
| <30 | 161 | 95 | 59.0 | 148 | 93 | 62.8 | 0.4906 | 1.06 | (0.89, 1.27) | 1.17 | (0.74,1.86) | 0.04 | (-0.07, 0.15) | |
| 30 to <45 | 550 | 313 | 56.9 | 564 | 285 | 50.5 | 0.0328 | 0.89 | (0.80, 0.99) | 0.77 | (0.61,0.98) | -0.06 | (-0.12,-0.01) | |
| >=45 | 1289 | 579 | 44.9 | 1340 | 579 | 43.2 | 0.3774 | 0.96 | (0.88, 1.05) | 0.93 | (0.80,1.09) | -0.02 | (-0.06, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7176 |
| Normal (<30) | 764 | 362 | 47.4 | 787 | 354 | 45.0 | 0.3429 | 0.95 | (0.85, 1.06) | 0.91 | (0.74,1.11) | -0.02 | (-0.07, 0.03) | |
| Microalbuminuria (30 to <=300) | 921 | 451 | 49.0 | 938 | 444 | 47.3 | 0.4809 | 0.97 | (0.88, 1.06) | 0.94 | (0.78,1.12) | -0.02 | (-0.06, 0.03) | |
| Macroalbuminuria (>300) | 311 | 172 | 55.3 | 318 | 158 | 49.7 | 0.1582 | 0.90 | (0.77, 1.04) | 0.80 | (0.58,1.09) | -0.06 | (-0.13, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7703 |
| Low, moderate or high | 1477 | 682 | 46.2 | 1548 | 684 | 44.2 | 0.2719 | 0.96 | (0.88, 1.04) | 0.92 | (0.80,1.06) | -0.02 | (-0.06, 0.02) | |
| Very high | 519 | 304 | 58.6 | 495 | 272 | 54.9 | 0.2441 | 0.94 | (0.84, 1.04) | 0.86 | (0.67,1.11) | -0.04 | (-0.10, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7231 |
| No | 411 | 221 | 53.8 | 410 | 213 | 52.0 | 0.6014 | 0.97 | (0.85, 1.10) | 0.93 | (0.71,1.22) | -0.02 | (-0.09, 0.05) | |
| Yes | 1590 | 766 | 48.2 | 1642 | 744 | 45.3 | 0.1026 | 0.94 | (0.87, 1.01) | 0.89 | (0.78,1.02) | -0.03 | (-0.06, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9828 |
| No | 282 | 144 | 51.1 | 277 | 134 | 48.4 | 0.5250 | 0.95 | (0.80, 1.12) | 0.90 | (0.64,1.25) | -0.03 | (-0.11, 0.06) | |
| Yes | 1719 | 843 | 49.0 | 1775 | 823 | 46.4 | 0.1136 | 0.95 | (0.88, 1.01) | 0.90 | (0.79,1.03) | -0.03 | (-0.06, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4693 |
| No | 229 | 106 | 46.3 | 250 | 102 | 40.8 | 0.2261 | 0.88 | (0.72, 1.08) | 0.80 | (0.56,1.15) | -0.05 | (-0.14, 0.03) | |
| Yes | 1772 | 881 | 49.7 | 1802 | 855 | 47.4 | 0.1745 | 0.95 | (0.89, 1.02) | 0.91 | (0.80,1.04) | -0.02 | (-0.06, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 5 Proportion of patients with severe adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 739 | 36.9 | 2052 | 720 | 35.1 | 0.2215 | 0.95 | (0.88,1.03) | 0.92 | (0.81,1.05) | -0.02 | (-0.05,0.01) | |
| Sex | | | | | | | | | | | | | | 0.5297 |
| Male | 1065 | 417 | 39.2 | 1093 | 416 | 38.1 | 0.6016 | 0.97 | (0.87,1.08) | 0.95 | (0.80,1.14) | -0.01 | (-0.05,0.03) | |
| Female | 936 | 322 | 34.4 | 959 | 304 | 31.7 | 0.2112 | 0.92 | (0.81,1.05) | 0.89 | (0.73,1.07) | -0.03 | (-0.07,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.9281 |
| <65 | 331 | 118 | 35.6 | 313 | 105 | 33.5 | 0.5750 | 0.94 | (0.76,1.16) | 0.91 | (0.66,1.26) | -0.02 | (-0.09,0.05) | |
| >=65 | 1670 | 621 | 37.2 | 1739 | 615 | 35.4 | 0.2690 | 0.95 | (0.87,1.04) | 0.92 | (0.80,1.06) | -0.02 | (-0.05,0.01) | |
| Region | | | | | | | | | | | | | | 0.5334 |
| North America | 273 | 127 | 46.5 | 273 | 138 | 50.5 | 0.3462 | 1.09 | (0.91,1.29) | 1.18 | (0.84,1.64) | 0.04 | (-0.04,0.12) | |
| Latin America | 511 | 210 | 41.1 | 504 | 191 | 37.9 | 0.2972 | 0.92 | (0.79,1.07) | 0.87 | (0.68,1.13) | -0.03 | (-0.09,0.03) | |
| Europe | 865 | 272 | 31.4 | 894 | 268 | 30.0 | 0.5047 | 0.95 | (0.83,1.10) | 0.93 | (0.76,1.14) | -0.01 | (-0.06,0.03) | |
| Asia | 231 | 76 | 32.9 | 248 | 70 | 28.2 | 0.2668 | 0.86 | (0.65,1.12) | 0.80 | (0.54,1.18) | -0.05 | (-0.13,0.04) | |
| Other | 121 | 54 | 44.6 | 133 | 53 | 39.8 | 0.4411 | 0.89 | (0.67,1.19) | 0.82 | (0.50,1.35) | -0.05 | (-0.17,0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8161 |
| Diabetic | 1045 | 418 | 40.0 | 1081 | 407 | 37.7 | 0.2664 | 0.94 | (0.85,1.05) | 0.91 | (0.76,1.08) | -0.02 | (-0.06,0.02) | |
| Non-Diabetic | 956 | 321 | 33.6 | 971 | 313 | 32.2 | 0.5306 | 0.96 | (0.85,1.09) | 0.94 | (0.78,1.14) | -0.01 | (-0.06,0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2185 |
| <30 | 1086 | 412 | 37.9 | 1094 | 376 | 34.4 | 0.0829 | 0.91 | (0.81,1.01) | 0.86 | (0.72,1.02) | -0.04 | (-0.08,0.00) | |
| >=30 | 915 | 327 | 35.7 | 958 | 344 | 35.9 | 0.9387 | 1.00 | (0.89,1.13) | 1.01 | (0.83,1.22) | 0.00 | (-0.04,0.05) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7773 |
| <130 | 827 | 309 | 37.4 | 853 | 307 | 36.0 | 0.5592 | 0.96 | (0.85,1.09) | 0.94 | (0.77,1.15) | -0.01 | (-0.06,0.03) | |
| >=130 | 1174 | 430 | 36.6 | 1199 | 413 | 34.4 | 0.2669 | 0.94 | (0.84,1.05) | 0.91 | (0.77,1.08) | -0.02 | (-0.06,0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5977 |
| <75 | 935 | 371 | 39.7 | 934 | 342 | 36.6 | 0.1729 | 0.92 | (0.82,1.04) | 0.88 | (0.73,1.06) | -0.03 | (-0.07,0.01) | |
| 75 to <85 | 657 | 238 | 36.2 | 703 | 241 | 34.3 | 0.4533 | 0.95 | (0.82,1.09) | 0.92 | (0.74,1.15) | -0.02 | (-0.07,0.03) | |
| >=85 | 409 | 130 | 31.8 | 415 | 137 | 33.0 | 0.7067 | 1.04 | (0.85,1.27) | 1.06 | (0.79,1.42) | 0.01 | (-0.05,0.08) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 5 Proportion of patients with severe adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3830 |
| <30 | 161 | 102 | 63.4 | 148 | 79 | 53.4 | 0.0753 | 0.84 | (0.70,1.02) | 0.66 | (0.42,1.04) | -0.10 | (-0.21,0.01) | |
| 30 to <45 | 550 | 226 | 41.1 | 564 | 220 | 39.0 | 0.4779 | 0.95 | (0.82,1.10) | 0.92 | (0.72,1.17) | -0.02 | (-0.08,0.04) | |
| >=45 | 1289 | 411 | 31.9 | 1340 | 421 | 31.4 | 0.7968 | 0.99 | (0.88,1.10) | 0.98 | (0.83,1.15) | 0.00 | (-0.04,0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8133 |
| Normal (<30) | 764 | 240 | 31.4 | 787 | 235 | 29.9 | 0.5070 | 0.95 | (0.82,1.10) | 0.93 | (0.75,1.15) | -0.02 | (-0.06,0.03) | |
| Microalbuminuria (30 to <=300) | 921 | 348 | 37.8 | 938 | 346 | 36.9 | 0.6890 | 0.98 | (0.87,1.10) | 0.96 | (0.80,1.16) | -0.01 | (-0.05,0.03) | |
| Macroalbuminuria (>300) | 311 | 149 | 47.9 | 318 | 139 | 43.7 | 0.2906 | 0.91 | (0.77,1.08) | 0.84 | (0.62,1.16) | -0.04 | (-0.12,0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5438 |
| Low, moderate or high | 1477 | 472 | 32.0 | 1548 | 484 | 31.3 | 0.6830 | 0.98 | (0.88,1.09) | 0.97 | (0.83,1.13) | -0.01 | (-0.04,0.03) | |
| Very high | 519 | 266 | 51.3 | 495 | 236 | 47.7 | 0.2550 | 0.93 | (0.82,1.05) | 0.87 | (0.68,1.11) | -0.04 | (-0.10,0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3808 |
| No | 411 | 170 | 41.4 | 410 | 172 | 42.0 | 0.8642 | 1.01 | (0.86,1.19) | 1.02 | (0.78,1.35) | 0.01 | (-0.06,0.07) | |
| Yes | 1590 | 569 | 35.8 | 1642 | 548 | 33.4 | 0.1494 | 0.93 | (0.85,1.03) | 0.90 | (0.78,1.04) | -0.02 | (-0.06,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9764 |
| No | 282 | 110 | 39.0 | 277 | 103 | 37.2 | 0.6572 | 0.95 | (0.77,1.18) | 0.93 | (0.66,1.30) | -0.02 | (-0.10,0.06) | |
| Yes | 1719 | 629 | 36.6 | 1775 | 617 | 34.8 | 0.2588 | 0.95 | (0.87,1.04) | 0.92 | (0.80,1.06) | -0.02 | (-0.05,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4155 |
| No | 229 | 73 | 31.9 | 250 | 68 | 27.2 | 0.2618 | 0.85 | (0.65,1.13) | 0.80 | (0.54,1.18) | -0.05 | (-0.13,0.03) | |
| Yes | 1772 | 666 | 37.6 | 1802 | 652 | 36.2 | 0.3849 | 0.96 | (0.88,1.05) | 0.94 | (0.82,1.08) | -0.01 | (-0.05,0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 448 | 22.4 | 2052 | 496 | 24.2 | 0.1795 | 1.08 | ( 0.97,1.21) | 1.11 | (0.96,1.28) | 0.02 | (-0.01,0.04) | |
| Sex | | | | | | | | | | | | | | 0.8307 |
| Male | 1065 | 250 | 23.5 | 1093 | 280 | 25.6 | 0.2475 | 1.09 | ( 0.94,1.27) | 1.12 | (0.92,1.37) | 0.02 | (-0.01,0.06) | |
| Female | 936 | 198 | 21.2 | 959 | 216 | 22.5 | 0.4707 | 1.06 | ( 0.90,1.26) | 1.08 | (0.87,1.35) | 0.01 | (-0.02,0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.9547 |
| <65 | 331 | 71 | 21.5 | 313 | 73 | 23.3 | 0.5687 | 1.09 | ( 0.82,1.45) | 1.11 | (0.77,1.61) | 0.02 | (-0.05,0.08) | |
| >=65 | 1670 | 377 | 22.6 | 1739 | 423 | 24.3 | 0.2282 | 1.08 | ( 0.95,1.22) | 1.10 | (0.94,1.29) | 0.02 | (-0.01,0.05) | |
| Region | | | | | | | | | | | | | | 0.6683 |
| North America | 273 | 93 | 34.1 | 273 | 111 | 40.7 | 0.1113 | 1.19 | ( 0.96,1.49) | 1.33 | (0.94,1.88) | 0.07 | (-0.02,0.15) | |
| Latin America | 511 | 130 | 25.4 | 504 | 124 | 24.6 | 0.7582 | 0.97 | ( 0.78,1.20) | 0.96 | (0.72,1.27) | -0.01 | (-0.06,0.04) | |
| Europe | 865 | 150 | 17.3 | 894 | 178 | 19.9 | 0.1666 | 1.15 | ( 0.94,1.40) | 1.19 | (0.93,1.51) | 0.03 | (-0.01,0.06) | |
| Asia | 231 | 41 | 17.7 | 248 | 45 | 18.1 | 0.9101 | 1.02 | ( 0.70,1.50) | 1.03 | (0.64,1.64) | 0.00 | (-0.06,0.07) | |
| Other | 121 | 34 | 28.1 | 133 | 38 | 28.6 | 0.9335 | 1.02 | ( 0.69,1.50) | 1.02 | (0.59,1.77) | 0.00 | (-0.11,0.12) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7884 |
| Diabetic | 1045 | 252 | 24.1 | 1081 | 285 | 26.4 | 0.2327 | 1.09 | ( 0.94,1.27) | 1.13 | (0.93,1.37) | 0.02 | (-0.01,0.06) | |
| Non-Diabetic | 956 | 196 | 20.5 | 971 | 211 | 21.7 | 0.5090 | 1.06 | ( 0.89,1.26) | 1.08 | (0.86,1.34) | 0.01 | (-0.02,0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3478 |
| <30 | 1086 | 234 | 21.5 | 1094 | 241 | 22.0 | 0.7851 | 1.02 | ( 0.87,1.20) | 1.03 | (0.84,1.26) | 0.00 | (-0.03,0.04) | |
| >=30 | 915 | 214 | 23.4 | 958 | 255 | 26.6 | 0.1068 | 1.14 | ( 0.97,1.33) | 1.19 | (0.96,1.47) | 0.03 | (-0.01,0.07) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9994 |
| <130 | 827 | 194 | 23.5 | 853 | 216 | 25.3 | 0.3738 | 1.08 | ( 0.91,1.28) | 1.11 | (0.89,1.38) | 0.02 | (-0.02,0.06) | |
| >=130 | 1174 | 254 | 21.6 | 1199 | 280 | 23.4 | 0.3165 | 1.08 | ( 0.93,1.25) | 1.10 | (0.91,1.34) | 0.02 | (-0.02,0.05) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9988 |
| <75 | 935 | 223 | 23.9 | 934 | 240 | 25.7 | 0.3554 | 1.08 | ( 0.92,1.26) | 1.10 | (0.89,1.36) | 0.02 | (-0.02,0.06) | |
| 75 to <85 | 657 | 146 | 22.2 | 703 | 169 | 24.0 | 0.4272 | 1.08 | ( 0.89,1.31) | 1.11 | (0.86,1.43) | 0.02 | (-0.03,0.06) | |
| >=85 | 409 | 79 | 19.3 | 415 | 87 | 21.0 | 0.5553 | 1.09 | ( 0.83,1.42) | 1.11 | (0.79,1.56) | 0.02 | (-0.04,0.07) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2597 |
| <30 | 161 | 72 | 44.7 | 148 | 60 | 40.5 | 0.4581 | 0.91 | ( 0.70,1.18) | 0.84 | (0.54,1.32) | -0.04 | (-0.15,0.07) | |
| 30 to <45 | 550 | 142 | 25.8 | 564 | 153 | 27.1 | 0.6204 | 1.05 | ( 0.86,1.28) | 1.07 | (0.82,1.40) | 0.01 | (-0.04,0.06) | |
| >=45 | 1289 | 234 | 18.2 | 1340 | 283 | 21.1 | 0.0558 | 1.16 | (<1.00,1.36) | 1.21 | (1.00,1.46) | 0.03 | ( 0.00,0.06) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3212 |
| Normal (<30) | 764 | 157 | 20.5 | 787 | 168 | 21.3 | 0.6998 | 1.04 | ( 0.86,1.26) | 1.05 | (0.82,1.34) | 0.01 | (-0.03,0.05) | |
| Microalbuminuria (30 to <=300) | 921 | 199 | 21.6 | 938 | 240 | 25.6 | 0.0434 | 1.18 | (>1.00,1.40) | 1.25 | (1.01,1.55) | 0.04 | ( 0.00,0.08) | |
| Macroalbuminuria (>300) | 311 | 90 | 28.9 | 318 | 88 | 27.7 | 0.7245 | 0.96 | ( 0.75,1.23) | 0.94 | (0.66,1.33) | -0.01 | (-0.08,0.06) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2604 |
| Low, moderate or high | 1477 | 280 | 19.0 | 1548 | 336 | 21.7 | 0.0606 | 1.14 | ( 0.99,1.32) | 1.19 | (0.99,1.42) | 0.03 | ( 0.00,0.06) | |
| Very high | 519 | 167 | 32.2 | 495 | 160 | 32.3 | 0.9604 | 1.00 | ( 0.84,1.20) | 1.01 | (0.77,1.31) | 0.00 | (-0.06,0.06) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4703 |
| No | 411 | 108 | 26.3 | 410 | 125 | 30.5 | 0.1809 | 1.16 | ( 0.93,1.44) | 1.23 | (0.91,1.67) | 0.04 | (-0.02,0.10) | |
| Yes | 1590 | 340 | 21.4 | 1642 | 371 | 22.6 | 0.4061 | 1.06 | ( 0.93,1.20) | 1.07 | (0.91,1.27) | 0.01 | (-0.02,0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9989 |
| No | 282 | 66 | 23.4 | 277 | 70 | 25.3 | 0.6071 | 1.08 | ( 0.81,1.45) | 1.11 | (0.75,1.63) | 0.02 | (-0.05,0.09) | |
| Yes | 1719 | 382 | 22.2 | 1775 | 426 | 24.0 | 0.2128 | 1.08 | ( 0.96,1.22) | 1.11 | (0.94,1.29) | 0.02 | (-0.01,0.05) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6937 |
| No | 229 | 41 | 17.9 | 250 | 45 | 18.0 | 0.9782 | 1.01 | ( 0.69,1.47) | 1.01 | (0.63,1.61) | 0.00 | (-0.07,0.07) | |
| Yes | 1772 | 407 | 23.0 | 1802 | 451 | 25.0 | 0.1495 | 1.09 | ( 0.97,1.22) | 1.12 | (0.96,1.31) | 0.02 | (-0.01,0.05) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.2.2.2**

R.2.2.2 Adverse events leading to treatment discontinuation

Table R.2.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 437 | 21.8 | 2052 | 445 | 21.7 | 0.9061 | 0.99 | (0.88,1.12) | 0.99 | (0.85,1.15) | 0.00 | (-0.03,0.02) | |
| Sex | | | | | | | | | | | | | | 0.9205 |
| Male | 1065 | 246 | 23.1 | 1093 | 252 | 23.1 | 0.9812 | 1.00 | (0.86,1.16) | 1.00 | (0.82,1.22) | 0.00 | (-0.04,0.04) | |
| Female | 936 | 191 | 20.4 | 959 | 193 | 20.1 | 0.8791 | 0.99 | (0.82,1.18) | 0.98 | (0.79,1.23) | 0.00 | (-0.04,0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.6982 |
| <65 | 331 | 72 | 21.8 | 313 | 64 | 20.4 | 0.6851 | 0.94 | (0.70,1.27) | 0.92 | (0.63,1.35) | -0.01 | (-0.08,0.05) | |
| >=65 | 1670 | 365 | 21.9 | 1739 | 381 | 21.9 | 0.9702 | 1.00 | (0.88,1.14) | 1.00 | (0.85,1.18) | 0.00 | (-0.03,0.03) | |
| Region | | | | | | | | | | | | | | 0.5214 |
| North America | 273 | 63 | 23.1 | 273 | 76 | 27.8 | 0.2016 | 1.21 | (0.90,1.61) | 1.29 | (0.87,1.89) | 0.05 | (-0.03,0.12) | |
| Latin America | 511 | 130 | 25.4 | 504 | 117 | 23.2 | 0.4086 | 0.91 | (0.73,1.13) | 0.89 | (0.66,1.18) | -0.02 | (-0.08,0.03) | |
| Europe | 865 | 182 | 21.0 | 894 | 177 | 19.8 | 0.5183 | 0.94 | (0.78,1.13) | 0.93 | (0.73,1.17) | -0.01 | (-0.05,0.03) | |
| Asia | 231 | 31 | 13.4 | 248 | 38 | 15.3 | 0.5535 | 1.14 | (0.74,1.77) | 1.17 | (0.70,1.95) | 0.02 | (-0.04,0.08) | |
| Other | 121 | 31 | 25.6 | 133 | 37 | 27.8 | 0.6925 | 1.09 | (0.72,1.63) | 1.12 | (0.64,1.95) | 0.02 | (-0.09,0.13) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5262 |
| Diabetic | 1045 | 238 | 22.8 | 1081 | 236 | 21.8 | 0.6013 | 0.96 | (0.82,1.12) | 0.95 | (0.77,1.16) | -0.01 | (-0.04,0.03) | |
| Non-Diabetic | 956 | 199 | 20.8 | 971 | 209 | 21.5 | 0.7036 | 1.03 | (0.87,1.23) | 1.04 | (0.84,1.30) | 0.01 | (-0.03,0.04) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2758 |
| <30 | 1086 | 252 | 23.2 | 1094 | 238 | 21.8 | 0.4176 | 0.94 | (0.80,1.10) | 0.92 | (0.75,1.13) | -0.01 | (-0.05,0.02) | |
| >=30 | 915 | 185 | 20.2 | 958 | 207 | 21.6 | 0.4601 | 1.07 | (0.90,1.27) | 1.09 | (0.87,1.36) | 0.01 | (-0.02,0.05) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1675 |
| <130 | 827 | 164 | 19.8 | 853 | 186 | 21.8 | 0.3191 | 1.10 | (0.91,1.33) | 1.13 | (0.89,1.43) | 0.02 | (-0.02,0.06) | |
| >=130 | 1174 | 273 | 23.3 | 1199 | 259 | 21.6 | 0.3345 | 0.93 | (0.80,1.08) | 0.91 | (0.75,1.10) | -0.02 | (-0.05,0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7665 |
| <75 | 935 | 209 | 22.4 | 934 | 202 | 21.6 | 0.7049 | 0.97 | (0.82,1.15) | 0.96 | (0.77,1.19) | -0.01 | (-0.04,0.03) | |
| 75 to <85 | 657 | 140 | 21.3 | 703 | 158 | 22.5 | 0.6034 | 1.05 | (0.86,1.29) | 1.07 | (0.83,1.38) | 0.01 | (-0.03,0.06) | |
| >=85 | 409 | 88 | 21.5 | 415 | 85 | 20.5 | 0.7156 | 0.95 | (0.73,1.24) | 0.94 | (0.67,1.31) | -0.01 | (-0.07,0.05) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2728 |
| <30 | 161 | 64 | 39.8 | 148 | 48 | 32.4 | 0.1812 | 0.82 | (0.60,1.10) | 0.73 | (0.46,1.16) | -0.07 | (-0.18,0.03) | |
| 30 to <45 | 550 | 119 | 21.6 | 564 | 135 | 23.9 | 0.3603 | 1.11 | (0.89,1.37) | 1.14 | (0.86,1.51) | 0.02 | (-0.03,0.07) | |
| >=45 | 1289 | 254 | 19.7 | 1340 | 262 | 19.6 | 0.9214 | 0.99 | (0.85,1.16) | 0.99 | (0.82,1.20) | 0.00 | (-0.03,0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3017 |
| Normal (<30) | 764 | 133 | 17.4 | 787 | 141 | 17.9 | 0.7932 | 1.03 | (0.83,1.28) | 1.04 | (0.80,1.34) | 0.01 | (-0.03,0.04) | |
| Microalbuminuria (30 to <=300) | 921 | 202 | 21.9 | 938 | 217 | 23.1 | 0.5353 | 1.05 | (0.89,1.25) | 1.07 | (0.86,1.33) | 0.01 | (-0.03,0.05) | |
| Macroalbuminuria (>300) | 311 | 101 | 32.5 | 318 | 87 | 27.4 | 0.1610 | 0.84 | (0.66,1.07) | 0.78 | (0.56,1.10) | -0.05 | (-0.12,0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7861 |
| Low, moderate or high | 1477 | 281 | 19.0 | 1548 | 293 | 18.9 | 0.9456 | 0.99 | (0.86,1.15) | 0.99 | (0.83,1.19) | 0.00 | (-0.03,0.03) | |
| Very high | 519 | 155 | 29.9 | 495 | 152 | 30.7 | 0.7705 | 1.03 | (0.85,1.24) | 1.04 | (0.80,1.36) | 0.01 | (-0.05,0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7914 |
| No | 411 | 97 | 23.6 | 410 | 99 | 24.1 | 0.8546 | 1.02 | (0.80,1.31) | 1.03 | (0.75,1.42) | 0.01 | (-0.05,0.06) | |
| Yes | 1590 | 340 | 21.4 | 1642 | 346 | 21.1 | 0.8284 | 0.99 | (0.86,1.13) | 0.98 | (0.83,1.16) | 0.00 | (-0.03,0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4970 |
| No | 282 | 72 | 25.5 | 277 | 64 | 23.1 | 0.5037 | 0.90 | (0.68,1.21) | 0.88 | (0.60,1.29) | -0.02 | (-0.10,0.05) | |
| Yes | 1719 | 365 | 21.2 | 1775 | 381 | 21.5 | 0.8674 | 1.01 | (0.89,1.15) | 1.01 | (0.86,1.19) | 0.00 | (-0.02,0.03) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6486 |
| No | 229 | 45 | 19.7 | 250 | 45 | 18.0 | 0.6441 | 0.92 | (0.63,1.33) | 0.90 | (0.57,1.42) | -0.02 | (-0.09,0.05) | |
| Yes | 1772 | 392 | 22.1 | 1802 | 400 | 22.2 | 0.9566 | 1.00 | (0.89,1.13) | 1.00 | (0.86,1.18) | 0.00 | (-0.03,0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Number of patients | 2001 (100.0) | | | 2052 (100.0) | | |
| Total with adverse events | 437 ( 21.8) | 3992.42 | 10.95 | 445 ( 21.7) | 4096.87 | 10.86 |
| Cardiac disorders | 106 ( 5.3) | 4235.56 | 2.50 | 87 ( 4.2) | 4341.33 | 2.00 |
| Cardiac failure | 58 ( 2.9) | 4246.23 | 1.37 | 40 ( 1.9) | 4354.85 | 0.92 |
| Myocardial infarction | 9 ( 0.4) | 4267.85 | 0.21 | 7 ( 0.3) | 4367.65 | 0.16 |
| Acute myocardial infarction | 8 ( 0.4) | 4267.50 | 0.19 | 8 ( 0.4) | 4366.86 | 0.18 |
| Cardiac failure congestive | 8 ( 0.4) | 4263.97 | 0.19 | 6 ( 0.3) | 4364.28 | 0.14 |
| Cardiac arrest | 4 ( 0.2) | 4267.98 | 0.09 | 7 ( 0.3) | 4366.97 | 0.16 |
| Cardiac failure acute | 5 ( 0.2) | 4267.82 | 0.12 | 1 ( <0.1) | 4367.75 | 0.02 |
| Cardiogenic shock | 4 ( 0.2) | 4267.98 | 0.09 | 2 ( 0.1) | 4367.76 | 0.05 |
| Atrial fibrillation | 1 ( <0.1) | 4267.42 | 0.02 | 4 ( 0.2) | 4366.51 | 0.09 |
| Cardio-respiratory arrest | 0 | 4267.98 | 0 | 3 ( 0.1) | 4367.73 | 0.07 |
| Cardiac failure chronic | 2 ( 0.1) | 4267.77 | 0.05 | 1 ( <0.1) | 4367.74 | 0.02 |
| Cardiopulmonary failure | 1 ( <0.1) | 4267.98 | 0.02 | 2 ( 0.1) | 4367.76 | 0.05 |
| Angina pectoris | 1 ( <0.1) | 4265.34 | 0.02 | 0 | 4367.76 | 0 |
| Aortic valve stenosis | 1 ( <0.1) | 4267.64 | 0.02 | 0 | 4367.76 | 0 |
| Arrhythmia | 1 ( <0.1) | 4267.12 | 0.02 | 0 | 4367.76 | 0 |
| Coronary artery disease | 1 ( <0.1) | 4267.95 | 0.02 | 0 | 4367.76 | 0 |
| Myocarditis | 1 ( <0.1) | 4267.96 | 0.02 | 0 | 4367.76 | 0 |
| Tachycardia | 1 ( <0.1) | 4266.79 | 0.02 | 1 ( <0.1) | 4365.29 | 0.02 |
| Acute left ventricular failure | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.72 | 0.02 |
| Aortic valve incompetence | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.74 | 0.02 |
| Atrioventricular block complete | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.55 | 0.02 |
| Atrioventricular block second degree | 0 | 4267.98 | 0 | 1 ( <0.1) | 4364.29 | 0.02 |
| Sinus node dysfunction | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.10 | 0.02 |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.2.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Infections and infestations | 62 ( 3.1) | 4247.16 | 1.46 | 77 ( 3.8) | 4327.10 | 1.78 |
| COVID-19 | 14 ( 0.7) | 4266.24 | 0.33 | 12 ( 0.6) | 4366.10 | 0.27 |
| Pneumonia | 10 ( 0.5) | 4265.25 | 0.23 | 12 ( 0.6) | 4366.63 | 0.27 |
| Urinary tract infection | 6 ( 0.3) | 4262.02 | 0.14 | 12 ( 0.6) | 4354.42 | 0.28 |
| COVID-19 pneumonia | 4 ( 0.2) | 4267.88 | 0.09 | 9 ( 0.4) | 4367.26 | 0.21 |
| Sepsis | 6 ( 0.3) | 4267.79 | 0.14 | 5 ( 0.2) | 4367.49 | 0.11 |
| Urosepsis | 5 ( 0.2) | 4265.36 | 0.12 | 2 ( 0.1) | 4365.18 | 0.05 |
| Septic shock | 3 ( 0.1) | 4267.86 | 0.07 | 2 ( 0.1) | 4367.75 | 0.05 |
| Bronchitis | 2 ( 0.1) | 4265.58 | 0.05 | 1 ( <0.1) | 4367.76 | 0.02 |
| Endocarditis | 1 ( <0.1) | 4267.29 | 0.02 | 2 ( 0.1) | 4364.75 | 0.05 |
| Fungal balanitis | 0 | 4267.98 | 0 | 2 ( 0.1) | 4365.98 | 0.05 |
| Anal infection | 1 ( <0.1) | 4267.48 | 0.02 | 1 ( <0.1) | 4367.68 | 0.02 |
| Cholecystitis infective | 1 ( <0.1) | 4267.96 | 0.02 | 0 | 4367.76 | 0 |
| Clostridium difficile infection | 1 ( <0.1) | 4267.90 | 0.02 | 0 | 4367.76 | 0 |
| Gangrene | 1 ( <0.1) | 4266.81 | 0.02 | 1 ( <0.1) | 4366.67 | 0.02 |
| Gastroenteritis | 1 ( <0.1) | 4267.92 | 0.02 | 0 | 4367.76 | 0 |
| Hepatitis A | 1 ( <0.1) | 4267.89 | 0.02 | 0 | 4367.76 | 0 |
| Influenza | 1 ( <0.1) | 4267.98 | 0.02 | 1 ( <0.1) | 4365.80 | 0.02 |
| Liver abscess | 1 ( <0.1) | 4266.04 | 0.02 | 0 | 4367.76 | 0 |
| Peritonsillitis | 1 ( <0.1) | 4267.96 | 0.02 | 0 | 4367.76 | 0 |
| Pneumonia viral | 1 ( <0.1) | 4267.72 | 0.02 | 0 | 4367.76 | 0 |
| Tracheobronchitis | 1 ( <0.1) | 4267.95 | 0.02 | 0 | 4367.76 | 0 |
| Vulvovaginal candidiasis | 1 ( <0.1) | 4267.69 | 0.02 | 1 ( <0.1) | 4365.08 | 0.02 |
| Appendicitis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.70 | 0.02 |
| Atypical pneumonia | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.70 | 0.02 |
| Balanitis candida | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.37 | 0.02 |
| Cellulitis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.64 | 0.02 |
| Cholangitis infective | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.66 | 0.02 |
| Chronic sinusitis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.86 | 0.02 |
| Diverticulitis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.61 | 0.02 |
| Fournier’s gangrene | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.57 | 0.02 |
| Genital infection | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.67 | 0.02 |
| Labyrinthitis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.60 | 0.02 |
| Lung abscess | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.68 | 0.02 |
| Penile infection | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.76 | 0.02 |
| Periodontitis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4365.86 | 0.02 |
| Pneumonia aspiration | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.75 | 0.02 |
| Postoperative abscess | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.49 | 0.02 |
| Pyelonephritis acute | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.76 | 0.02 |
| Small intestine gangrene | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.75 | 0.02 |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.2.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| General disorders and administration site conditions | 49 ( 2.4) | 4245.96 | 1.15 | 62 ( 3.0) | 4356.13 | 1.42 |
| Death | 22 ( 1.1) | 4267.79 | 0.52 | 43 ( 2.1) | 4366.86 | 0.98 |
| Sudden cardiac death | 7 ( 0.3) | 4267.98 | 0.16 | 3 ( 0.1) | 4367.76 | 0.07 |
| Sudden death | 6 ( 0.3) | 4267.98 | 0.14 | 6 ( 0.3) | 4367.76 | 0.14 |
| Cardiac death | 2 ( 0.1) | 4267.98 | 0.05 | 4 ( 0.2) | 4367.76 | 0.09 |
| Fatigue | 2 ( 0.1) | 4261.96 | 0.05 | 2 ( 0.1) | 4363.10 | 0.05 |
| Feeling cold | 2 ( 0.1) | 4262.92 | 0.05 | 0 | 4367.76 | 0 |
| Oedema peripheral | 2 ( 0.1) | 4263.17 | 0.05 | 0 | 4367.76 | 0 |
| Asthenia | 1 ( <0.1) | 4265.54 | 0.02 | 2 ( 0.1) | 4361.70 | 0.05 |
| Chest pain | 1 ( <0.1) | 4266.02 | 0.02 | 0 | 4367.76 | 0 |
| Multiple organ dysfunction syndrome | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Physical deconditioning | 1 ( <0.1) | 4267.87 | 0.02 | 0 | 4367.76 | 0 |
| Vascular stent occlusion | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Vessel puncture site reaction | 1 ( <0.1) | 4266.59 | 0.02 | 0 | 4367.76 | 0 |
| Accidental death | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.76 | 0.02 |
| Non-cardiac chest pain | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.76 | 0.02 |
| Renal and urinary disorders | 59 ( 2.9) | 4195.90 | 1.41 | 59 ( 2.9) | 4303.84 | 1.37 |
| Renal impairment | 20 ( 1.0) | 4240.76 | 0.47 | 21 ( 1.0) | 4344.36 | 0.48 |
| Acute kidney injury | 11 ( 0.5) | 4257.03 | 0.26 | 13 ( 0.6) | 4357.49 | 0.30 |
| Chronic kidney disease | 11 ( 0.5) | 4256.09 | 0.26 | 11 ( 0.5) | 4356.39 | 0.25 |
| Renal failure | 10 ( 0.5) | 4260.57 | 0.23 | 4 ( 0.2) | 4364.18 | 0.09 |
| Nocturia | 2 ( 0.1) | 4263.92 | 0.05 | 0 | 4367.76 | 0 |
| Polyuria | 0 | 4267.98 | 0 | 2 ( 0.1) | 4363.39 | 0.05 |
| Urinary incontinence | 1 ( <0.1) | 4265.49 | 0.02 | 2 ( 0.1) | 4363.97 | 0.05 |
| Bladder mass | 1 ( <0.1) | 4266.05 | 0.02 | 0 | 4367.76 | 0 |
| Diabetic nephropathy | 1 ( <0.1) | 4266.64 | 0.02 | 1 ( <0.1) | 4367.53 | 0.02 |
| Nephrolithiasis | 1 ( <0.1) | 4266.16 | 0.02 | 1 ( <0.1) | 4367.28 | 0.02 |
| Nephrosclerosis | 1 ( <0.1) | 4266.02 | 0.02 | 0 | 4367.76 | 0 |
| Renal colic | 1 ( <0.1) | 4266.13 | 0.02 | 0 | 4367.76 | 0 |
| Dysuria | 0 | 4267.98 | 0 | 1 ( <0.1) | 4365.79 | 0.02 |
| Hypertonic bladder | 0 | 4267.98 | 0 | 1 ( <0.1) | 4364.85 | 0.02 |
| Nephropathy | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.37 | 0.02 |
| Renal pain | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.64 | 0.02 |

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MedDRA version: 25.0

Table R.2.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Nervous system disorders | 42 ( 2.1) | 4232.19 | 0.99 | 49 ( 2.4) | 4331.18 | 1.13 |
| Ischaemic stroke | 12 ( 0.6) | 4259.57 | 0.28 | 11 ( 0.5) | 4363.15 | 0.25 |
| Dizziness | 8 ( 0.4) | 4254.02 | 0.19 | 4 ( 0.2) | 4359.36 | 0.09 |
| Cerebrovascular accident | 4 ( 0.2) | 4266.20 | 0.09 | 5 ( 0.2) | 4366.64 | 0.11 |
| Syncope | 1 ( <0.1) | 4267.78 | 0.02 | 5 ( 0.2) | 4364.86 | 0.11 |
| Haemorrhagic stroke | 4 ( 0.2) | 4266.15 | 0.09 | 4 ( 0.2) | 4365.39 | 0.09 |
| Dementia | 1 ( <0.1) | 4267.59 | 0.02 | 4 ( 0.2) | 4363.75 | 0.09 |
| Cerebral infarction | 2 ( 0.1) | 4266.90 | 0.05 | 0 | 4367.76 | 0 |
| Cerebral haemorrhage | 1 ( <0.1) | 4267.98 | 0.02 | 2 ( 0.1) | 4367.76 | 0.05 |
| Embolic stroke | 0 | 4267.98 | 0 | 2 ( 0.1) | 4366.77 | 0.05 |
| Altered state of consciousness | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Brain injury | 1 ( <0.1) | 4267.97 | 0.02 | 0 | 4367.76 | 0 |
| Cerebral artery embolism | 1 ( <0.1) | 4267.94 | 0.02 | 0 | 4367.76 | 0 |
| Cerebral artery occlusion | 1 ( <0.1) | 4266.90 | 0.02 | 0 | 4367.76 | 0 |
| Cerebral haematoma | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Embolic cerebral infarction | 1 ( <0.1) | 4265.18 | 0.02 | 0 | 4367.76 | 0 |
| Headache | 1 ( <0.1) | 4264.74 | 0.02 | 0 | 4367.76 | 0 |
| Lethargy | 1 ( <0.1) | 4265.99 | 0.02 | 0 | 4367.76 | 0 |
| Nervous system disorder | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Thalamus haemorrhage | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Cerebellar haematoma | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.28 | 0.02 |
| Cerebral arteriosclerosis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.26 | 0.02 |
| Cognitive disorder | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.53 | 0.02 |
| Dementia Alzheimer's type | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.76 | 0.02 |
| Haemorrhage intracranial | 0 | 4267.98 | 0 | 1 ( <0.1) | 4365.30 | 0.02 |
| Hypoaesthesia | 0 | 4267.98 | 0 | 1 ( <0.1) | 4365.55 | 0.02 |
| Hypoxic-ischaemic encephalopathy | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.74 | 0.02 |
| Intracranial aneurysm | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.54 | 0.02 |
| Parkinson's disease | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.66 | 0.02 |
| Postresuscitation encephalopathy | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.69 | 0.02 |
| Sciatica | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.73 | 0.02 |
| Transient ischaemic attack | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.60 | 0.02 |
| Tremor | 0 | 4267.98 | 0 | 1 ( <0.1) | 4364.90 | 0.02 |

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MedDRA version: 25.0

Table R.2.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 26 ( 1.3) | 4250.32 | 0.61 | 22 ( 1.1) | 4357.03 | 0.50 |
| Colon cancer metastatic | 2 ( 0.1) | 4266.72 | 0.05 | 0 | 4367.76 | 0 |
| Lung adenocarcinoma | 2 ( 0.1) | 4266.77 | 0.05 | 1 ( <0.1) | 4366.63 | 0.02 |
| Squamous cell carcinoma of lung | 2 ( 0.1) | 4264.61 | 0.05 | 0 | 4367.76 | 0 |
| Lung neoplasm malignant | 1 ( <0.1) | 4267.28 | 0.02 | 2 ( 0.1) | 4367.29 | 0.05 |
| Transitional cell carcinoma | 0 | 4267.98 | 0 | 2 ( 0.1) | 4365.55 | 0.05 |
| Bladder cancer | 1 ( <0.1) | 4267.93 | 0.02 | 0 | 4367.76 | 0 |
| Bladder transitional cell carcinoma | 1 ( <0.1) | 4267.39 | 0.02 | 0 | 4367.76 | 0 |
| Breast cancer female | 1 ( <0.1) | 4266.74 | 0.02 | 0 | 4367.76 | 0 |
| Colon cancer | 1 ( <0.1) | 4266.92 | 0.02 | 1 ( <0.1) | 4367.75 | 0.02 |
| Gastric neoplasm | 1 ( <0.1) | 4267.84 | 0.02 | 0 | 4367.76 | 0 |
| Hepatocellular carcinoma | 1 ( <0.1) | 4267.75 | 0.02 | 0 | 4367.76 | 0 |
| Laryngeal squamous cell carcinoma | 1 ( <0.1) | 4266.27 | 0.02 | 0 | 4367.76 | 0 |
| Leiomyosarcoma | 1 ( <0.1) | 4267.50 | 0.02 | 0 | 4367.76 | 0 |
| Lung neoplasm | 1 ( <0.1) | 4267.95 | 0.02 | 0 | 4367.76 | 0 |
| Mantle cell lymphoma | 1 ( <0.1) | 4265.62 | 0.02 | 0 | 4367.76 | 0 |
| Meningioma benign | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Myxoid liposarcoma | 1 ( <0.1) | 4266.69 | 0.02 | 0 | 4367.76 | 0 |
| Nasopharyngeal tumour | 1 ( <0.1) | 4267.72 | 0.02 | 0 | 4367.76 | 0 |
| Neoplasm malignant | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Oesophageal carcinoma | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Pancreatic carcinoma | 1 ( <0.1) | 4267.84 | 0.02 | 1 ( <0.1) | 4367.28 | 0.02 |
| Paraneoplastic syndrome | 1 ( <0.1) | 4267.38 | 0.02 | 0 | 4367.76 | 0 |
| Small cell lung cancer | 1 ( <0.1) | 4267.12 | 0.02 | 1 ( <0.1) | 4367.70 | 0.02 |
| Tongue neoplasm | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Acute lymphocytic leukaemia | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.73 | 0.02 |
| Adenocarcinoma metastatic | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.72 | 0.02 |
| Colorectal adenoma | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.32 | 0.02 |
| Intracranial tumour haemorrhage | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.75 | 0.02 |
| Laryngeal cancer | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.26 | 0.02 |
| Lung adenocarcinoma stage IV | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.63 | 0.02 |
| Metastatic bronchial carcinoma | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.75 | 0.02 |
| Myelodysplastic syndrome | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.97 | 0.02 |
| Nasal sinus cancer | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.94 | 0.02 |
| Non-Hodgkin’s lymphoma | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.66 | 0.02 |
| Non-small cell lung cancer metastatic | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.72 | 0.02 |
| Small intestine carcinoma | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.43 | 0.02 |
| Squamous cell carcinoma of the parotid gland | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.67 | 0.02 |

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MedDRA version: 25.0

Table R.2.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (cont.) | | | | | | |
| Vulval cancer | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.81 | 0.02 |
| Gastrointestinal disorders | 21 ( 1.0) | 4250.35 | 0.49 | 19 ( 0.9) | 4351.71 | 0.44 |
| Diarrhoea | 4 ( 0.2) | 4261.39 | 0.09 | 0 | 4367.76 | 0 |
| Dyspepsia | 3 ( 0.1) | 4265.72 | 0.07 | 1 ( <0.1) | 4365.56 | 0.02 |
| Nausea | 2 ( 0.1) | 4267.89 | 0.05 | 3 ( 0.1) | 4362.97 | 0.07 |
| Abdominal pain upper | 1 ( <0.1) | 4267.93 | 0.02 | 2 ( 0.1) | 4362.15 | 0.05 |
| Gastrointestinal haemorrhage | 1 ( <0.1) | 4266.26 | 0.02 | 2 ( 0.1) | 4367.69 | 0.05 |
| Vomiting | 0 | 4267.98 | 0 | 2 ( 0.1) | 4364.86 | 0.05 |
| Abdominal distension | 1 ( <0.1) | 4266.08 | 0.02 | 0 | 4367.76 | 0 |
| Abdominal pain | 1 ( <0.1) | 4266.84 | 0.02 | 0 | 4367.76 | 0 |
| Constipation | 1 ( <0.1) | 4266.57 | 0.02 | 0 | 4367.76 | 0 |
| Duodenal ulcer haemorrhage | 1 ( <0.1) | 4267.92 | 0.02 | 0 | 4367.76 | 0 |
| Gastrointestinal disorder | 1 ( <0.1) | 4265.48 | 0.02 | 0 | 4367.76 | 0 |
| Intestinal infarction | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Intestinal perforation | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Oesophageal haemorrhage | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Pancreatitis acute | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Small intestinal haemorrhage | 1 ( <0.1) | 4267.73 | 0.02 | 0 | 4367.76 | 0 |
| Swollen tongue | 1 ( <0.1) | 4266.98 | 0.02 | 0 | 4367.76 | 0 |
| Colitis ischaemic | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.75 | 0.02 |
| Diverticular perforation | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.76 | 0.02 |
| Gastrointestinal perforation | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.56 | 0.02 |
| Ileus | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.66 | 0.02 |
| Intestinal ischaemia | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.72 | 0.02 |
| Intestinal obstruction | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.76 | 0.02 |
| Lower gastrointestinal haemorrhage | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.76 | 0.02 |
| Mesenteric artery thrombosis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.69 | 0.02 |
| Upper gastrointestinal haemorrhage | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.76 | 0.02 |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.2.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Vascular disorders | 21 ( 1.0) | 4246.81 | 0.49 | 14 ( 0.7) | 4356.75 | 0.32 |
| Hypotension | 8 ( 0.4) | 4250.75 | 0.19 | 7 ( 0.3) | 4363.20 | 0.16 |
| Aortic aneurysm rupture | 2 ( 0.1) | 4267.82 | 0.05 | 0 | 4367.76 | 0 |
| Peripheral arterial occlusive disease | 2 ( 0.1) | 4267.28 | 0.05 | 1 ( <0.1) | 4366.12 | 0.02 |
| Aortic aneurysm | 1 ( <0.1) | 4267.97 | 0.02 | 0 | 4367.76 | 0 |
| Aortic dissection | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Aortic stenosis | 1 ( <0.1) | 4267.53 | 0.02 | 1 ( <0.1) | 4367.64 | 0.02 |
| Extremity necrosis | 1 ( <0.1) | 4267.84 | 0.02 | 1 ( <0.1) | 4366.61 | 0.02 |
| Haematoma | 1 ( <0.1) | 4267.89 | 0.02 | 0 | 4367.76 | 0 |
| Haemorrhagic infarction | 1 ( <0.1) | 4267.70 | 0.02 | 0 | 4367.76 | 0 |
| Hypertension | 1 ( <0.1) | 4267.90 | 0.02 | 0 | 4367.76 | 0 |
| Pallor | 1 ( <0.1) | 4265.99 | 0.02 | 0 | 4367.76 | 0 |
| Shock haemorrhagic | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Embolism | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.74 | 0.02 |
| Hot flush | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.48 | 0.02 |
| Thrombosis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4364.87 | 0.02 |
| Vasculitis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.45 | 0.02 |
| Respiratory, thoracic and mediastinal disorders | 15 ( 0.7) | 4264.95 | 0.35 | 8 ( 0.4) | 4367.36 | 0.18 |
| Chronic obstructive pulmonary disease | 3 ( 0.1) | 4267.93 | 0.07 | 1 ( <0.1) | 4367.76 | 0.02 |
| Respiratory failure | 2 ( 0.1) | 4267.86 | 0.05 | 3 ( 0.1) | 4367.52 | 0.07 |
| Acute respiratory distress syndrome | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Acute respiratory failure | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Choking | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Cough | 1 ( <0.1) | 4267.91 | 0.02 | 0 | 4367.76 | 0 |
| Dyspnoea | 1 ( <0.1) | 4266.65 | 0.02 | 1 ( <0.1) | 4367.76 | 0.02 |
| Haemoptysis | 1 ( <0.1) | 4267.04 | 0.02 | 0 | 4367.76 | 0 |
| Pulmonary arterial hypertension | 1 ( <0.1) | 4267.55 | 0.02 | 0 | 4367.76 | 0 |
| Pulmonary embolism | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Pulmonary oedema | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Respiratory disorder | 1 ( <0.1) | 4267.92 | 0.02 | 0 | 4367.76 | 0 |
| Interstitial lung disease | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.75 | 0.02 |
| Pulmonary hypertension | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.72 | 0.02 |
| Respiratory arrest | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.68 | 0.02 |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.2.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Metabolism and nutrition disorders | 14 ( 0.7) | 4254.68 | 0.33 | 8 ( 0.4) | 4361.62 | 0.18 |
| Hypoglycaemia | 3 ( 0.1) | 4265.06 | 0.07 | 1 ( <0.1) | 4364.89 | 0.02 |
| Decreased appetite | 2 ( 0.1) | 4265.92 | 0.05 | 0 | 4367.76 | 0 |
| Adult failure to thrive | 1 ( <0.1) | 4267.75 | 0.02 | 0 | 4367.76 | 0 |
| Dehydration | 1 ( <0.1) | 4267.93 | 0.02 | 1 ( <0.1) | 4366.20 | 0.02 |
| Diabetes mellitus | 1 ( <0.1) | 4266.72 | 0.02 | 1 ( <0.1) | 4367.23 | 0.02 |
| Diabetic ketoacidosis | 1 ( <0.1) | 4266.58 | 0.02 | 0 | 4367.76 | 0 |
| Gout | 1 ( <0.1) | 4266.30 | 0.02 | 1 ( <0.1) | 4367.46 | 0.02 |
| Hyperglycaemic hyperosmolar nonketotic syndrome | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Hypovolaemia | 1 ( <0.1) | 4266.28 | 0.02 | 0 | 4367.76 | 0 |
| Ketoacidosis | 1 ( <0.1) | 4266.59 | 0.02 | 1 ( <0.1) | 4367.76 | 0.02 |
| Metabolic acidosis | 1 ( <0.1) | 4267.41 | 0.02 | 1 ( <0.1) | 4367.65 | 0.02 |
| Cachexia | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.73 | 0.02 |
| Hyponatraemia | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.05 | 0.02 |
| Injury, poisoning and procedural complications | 8 ( 0.4) | 4264.17 | 0.19 | 11 ( 0.5) | 4365.06 | 0.25 |
| Fall | 2 ( 0.1) | 4267.93 | 0.05 | 1 ( <0.1) | 4367.61 | 0.02 |
| Femoral neck fracture | 1 ( <0.1) | 4267.97 | 0.02 | 0 | 4367.76 | 0 |
| Overdose | 1 ( <0.1) | 4267.49 | 0.02 | 0 | 4367.76 | 0 |
| Skin laceration | 1 ( <0.1) | 4267.70 | 0.02 | 0 | 4367.76 | 0 |
| Subdural haematoma | 1 ( <0.1) | 4267.98 | 0.02 | 1 ( <0.1) | 4367.71 | 0.02 |
| Subdural haemorrhage | 1 ( <0.1) | 4267.97 | 0.02 | 0 | 4367.76 | 0 |
| Upper limb fracture | 1 ( <0.1) | 4265.03 | 0.02 | 0 | 4367.76 | 0 |
| Craniocerebral injury | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.76 | 0.02 |
| Femur fracture | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.64 | 0.02 |
| Hip fracture | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.76 | 0.02 |
| Limb traumatic amputation | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.55 | 0.02 |
| Perineal injury | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.17 | 0.02 |
| Procedural complication | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.74 | 0.02 |
| Road traffic accident | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.76 | 0.02 |
| Traumatic spinal cord compression | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.51 | 0.02 |
| Wrist fracture | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.50 | 0.02 |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.2.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | 6 ( 0.3) | 4260.01 | 0.14 | 9 ( 0.4) | 4352.45 | 0.21 |
| Pruritus | 1 ( <0.1) | 4266.08 | 0.02 | 2 ( 0.1) | 4363.39 | 0.05 |
| Rash | 0 | 4267.98 | 0 | 2 ( 0.1) | 4364.28 | 0.05 |
| Diabetic foot | 1 ( <0.1) | 4266.77 | 0.02 | 0 | 4367.76 | 0 |
| Ecchymosis | 1 ( <0.1) | 4267.22 | 0.02 | 0 | 4367.76 | 0 |
| Hyperhidrosis | 1 ( <0.1) | 4264.75 | 0.02 | 0 | 4367.76 | 0 |
| Pyoderma gangrenosum | 1 ( <0.1) | 4267.73 | 0.02 | 0 | 4367.76 | 0 |
| Skin ulcer | 1 ( <0.1) | 4267.38 | 0.02 | 1 ( <0.1) | 4365.06 | 0.02 |
| Dermatitis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.47 | 0.02 |
| Eczema | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.23 | 0.02 |
| Granuloma annulare | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.38 | 0.02 |
| Rash erythematous | 0 | 4267.98 | 0 | 1 ( <0.1) | 4365.23 | 0.02 |
| Investigations | 8 ( 0.4) | 4258.35 | 0.19 | 7 ( 0.3) | 4356.88 | 0.16 |
| Glomerular filtration rate decreased | 1 ( <0.1) | 4265.51 | 0.02 | 4 ( 0.2) | 4362.36 | 0.09 |
| Blood bicarbonate decreased | 2 ( 0.1) | 4263.78 | 0.05 | 0 | 4367.76 | 0 |
| Blood creatinine increased | 2 ( 0.1) | 4267.10 | 0.05 | 2 ( 0.1) | 4364.27 | 0.05 |
| Alanine aminotransferase increased | 1 ( <0.1) | 4267.49 | 0.02 | 0 | 4367.76 | 0 |
| Aspartate aminotransferase increased | 1 ( <0.1) | 4267.49 | 0.02 | 0 | 4367.76 | 0 |
| Hepatic enzyme increased | 1 ( <0.1) | 4267.89 | 0.02 | 0 | 4367.76 | 0 |
| Liver function test abnormal | 1 ( <0.1) | 4266.49 | 0.02 | 0 | 4367.76 | 0 |
| Neutrophil count decreased | 0 | 4267.98 | 0 | 1 ( <0.1) | 4365.78 | 0.02 |
| Musculoskeletal and connective tissue disorders | 7 ( 0.3) | 4261.94 | 0.16 | 2 ( 0.1) | 4366.37 | 0.05 |
| Pain in extremity | 2 ( 0.1) | 4264.84 | 0.05 | 0 | 4367.76 | 0 |
| Flank pain | 1 ( <0.1) | 4267.91 | 0.02 | 0 | 4367.76 | 0 |
| Muscular weakness | 1 ( <0.1) | 4267.91 | 0.02 | 0 | 4367.76 | 0 |
| Myalgia | 1 ( <0.1) | 4266.07 | 0.02 | 0 | 4367.76 | 0 |
| Osteoarthritis | 1 ( <0.1) | 4267.33 | 0.02 | 0 | 4367.76 | 0 |
| Rheumatic disorder | 1 ( <0.1) | 4267.81 | 0.02 | 0 | 4367.76 | 0 |
| Polymyalgia rheumatica | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.38 | 0.02 |
| Sarcopenia | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.75 | 0.02 |

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Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.2.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Hepatobiliary disorders | 4 ( 0.2) | 4263.69 | 0.09 | 6 ( 0.3) | 4362.40 | 0.14 |
| Liver injury | 1 ( <0.1) | 4266.56 | 0.02 | 2 ( 0.1) | 4365.78 | 0.05 |
| Cholangitis | 1 ( <0.1) | 4267.97 | 0.02 | 0 | 4367.76 | 0 |
| Cholestasis | 1 ( <0.1) | 4265.14 | 0.02 | 1 ( <0.1) | 4367.25 | 0.02 |
| Hepatic function abnormal | 1 ( <0.1) | 4267.96 | 0.02 | 1 ( <0.1) | 4367.44 | 0.02 |
| Cholelithiasis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4365.83 | 0.02 |
| Liver disorder | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.15 | 0.02 |
| Psychiatric disorders | 4 ( 0.2) | 4264.52 | 0.09 | 4 ( 0.2) | 4362.02 | 0.09 |
| Completed suicide | 1 ( <0.1) | 4267.98 | 0.02 | 0 | 4367.76 | 0 |
| Confusional state | 1 ( <0.1) | 4267.97 | 0.02 | 0 | 4367.76 | 0 |
| Insomnia | 1 ( <0.1) | 4265.99 | 0.02 | 0 | 4367.76 | 0 |
| Nightmare | 1 ( <0.1) | 4266.53 | 0.02 | 0 | 4367.76 | 0 |
| Affect lability | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.46 | 0.02 |
| Alcoholism | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.23 | 0.02 |
| Depression | 0 | 4267.98 | 0 | 1 ( <0.1) | 4364.93 | 0.02 |
| Paranoia | 0 | 4267.98 | 0 | 1 ( <0.1) | 4366.70 | 0.02 |
| Blood and lymphatic system disorders | 3 ( 0.1) | 4267.82 | 0.07 | 1 ( <0.1) | 4367.47 | 0.02 |
| Coagulopathy | 1 ( <0.1) | 4267.89 | 0.02 | 0 | 4367.76 | 0 |
| Disseminated intravascular coagulation | 1 ( <0.1) | 4267.96 | 0.02 | 0 | 4367.76 | 0 |
| Thrombocytopenia | 1 ( <0.1) | 4267.93 | 0.02 | 0 | 4367.76 | 0 |
| Blood loss anaemia | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.47 | 0.02 |
| Ear and labyrinth disorders | 1 ( <0.1) | 4266.10 | 0.02 | 3 ( 0.1) | 4362.03 | 0.07 |
| Vertigo | 1 ( <0.1) | 4266.10 | 0.02 | 2 ( 0.1) | 4364.41 | 0.05 |
| Tinnitus | 0 | 4267.98 | 0 | 1 ( <0.1) | 4365.38 | 0.02 |
| Immune system disorders | 2 ( 0.1) | 4265.10 | 0.05 | 0 | 4367.76 | 0 |
| Corneal graft rejection | 1 ( <0.1) | 4267.70 | 0.02 | 0 | 4367.76 | 0 |
| Drug hypersensitivity | 1 ( <0.1) | 4265.38 | 0.02 | 0 | 4367.76 | 0 |
| Reproductive system and breast disorders | 1 ( <0.1) | 4267.17 | 0.02 | 2 ( 0.1) | 4366.68 | 0.05 |
| Benign prostatic hyperplasia | 1 ( <0.1) | 4267.17 | 0.02 | 0 | 4367.76 | 0 |
| Prostatitis | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.22 | 0.02 |
| Vulvovaginal pruritus | 0 | 4267.98 | 0 | 1 ( <0.1) | 4367.23 | 0.02 |
| Endocrine disorders | 1 ( <0.1) | 4267.87 | 0.02 | 0 | 4367.76 | 0 |
| Hyperthyroidism | 1 ( <0.1) | 4267.87 | 0.02 | 0 | 4367.76 | 0 |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

**R.2.2.3**

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 2001 | 22 | 1.1 | 2052 | 13 | 0.6 | 0.1090 | 0.58 ( 0.29, 1.14) | 0.57 ( 0.29, 1.14) | 0.00 (-0.01, 0.00) | | |
| Sex | | | | | | | | | | | | 0.1891 |
| Male | 1065 | 16 | 1.5 | 1093 | 12 | 1.1 | 0.4065 | 0.73 ( 0.35, 1.54) | 0.73 ( 0.34, 1.55) | 0.00 (-0.01, 0.01) | | |
| Female | 936 | 6 | 0.6 | 959 | 1 | 0.1 | 0.0541 | 0.16 ( 0.02, 1.35) | 0.16 ( 0.02, 1.35) | -0.01 (-0.01, 0.00) | | |
| Age [years] | | | | | | | | | | | | 0.4772 |
| <65 | 331 | 8 | 2.4 | 313 | 6 | 1.9 | 0.6637 | 0.79 ( 0.28, 2.26) | 0.79 ( 0.27, 2.30) | 0.00 (-0.03, 0.02) | | |
| >=65 | 1670 | 14 | 0.8 | 1739 | 7 | 0.4 | 0.1040 | 0.48 ( 0.19, 1.19) | 0.48 ( 0.19, 1.19) | 0.00 (-0.01, 0.00) | | |
| Region | | | | | | | | | | | | 0.9560 |
| North America | 273 | 5 | 1.8 | 273 | 4 | 1.5 | 0.7368 | 0.80 ( 0.22, 2.95) | 0.80 ( 0.21, 3.00) | 0.00 (-0.03, 0.02) | | |
| Latin America | 511 | 5 | 1.0 | 504 | 2 | 0.4 | 0.2629 | 0.41 ( 0.08, 2.08) | 0.40 ( 0.08, 2.09) | -0.01 (-0.02, 0.00) | | |
| Europe | 865 | 10 | 1.2 | 894 | 6 | 0.7 | 0.2842 | 0.58 ( 0.21, 1.59) | 0.58 ( 0.21, 1.60) | 0.00 (-0.01, 0.00) | | |
| Asia | 231 | 1 | 0.4 | 248 | 0 | 0 | 0.4478 | 0.31 ( 0.01, 7.59) | 0.31 ( 0.01, 7.63) | 0.00 (-0.02, 0.01) | | |
| Other | 121 | 1 | 0.8 | 133 | 1 | 0.8 | 0.9465 | 0.91 ( 0.06, 14.39) | 0.91 ( 0.06, 14.69) | 0.00 (-0.02, 0.02) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.8978 |
| Diabetic | 1045 | 20 | 1.9 | 1081 | 12 | 1.1 | 0.1281 | 0.58 ( 0.28, 1.18) | 0.58 ( 0.28, 1.18) | -0.01 (-0.02, 0.00) | | |
| Non-Diabetic | 956 | 2 | 0.2 | 971 | 1 | 0.1 | 0.5543 | 0.49 ( 0.04, 5.42) | 0.49 ( 0.04, 5.43) | 0.00 ( 0.00, 0.00) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2091 |
| <30 | 1086 | 10 | 0.9 | 1094 | 3 | 0.3 | 0.0499 | 0.30 ( 0.08, 1.08) | 0.30 ( 0.08, 1.08) | -0.01 (-0.01, 0.00) | | |
| >=30 | 915 | 12 | 1.3 | 958 | 10 | 1.0 | 0.5910 | 0.80 ( 0.35, 1.83) | 0.79 ( 0.34, 1.85) | 0.00 (-0.01, 0.01) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7255 |
| <130 | 827 | 8 | 1.0 | 853 | 4 | 0.5 | 0.2252 | 0.48 ( 0.15, 1.60) | 0.48 ( 0.14, 1.61) | 0.00 (-0.01, 0.00) | | |
| >=130 | 1174 | 14 | 1.2 | 1199 | 9 | 0.8 | 0.2720 | 0.63 ( 0.27, 1.45) | 0.63 ( 0.27, 1.45) | 0.00 (-0.01, 0.00) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5628 |
| <75 | 935 | 13 | 1.4 | 934 | 7 | 0.7 | 0.1782 | 0.54 ( 0.22, 1.34) | 0.54 ( 0.21, 1.35) | -0.01 (-0.02, 0.00) | | |
| 75 to <85 | 657 | 8 | 1.2 | 703 | 4 | 0.6 | 0.2012 | 0.47 ( 0.14, 1.54) | 0.46 ( 0.14, 1.55) | -0.01 (-0.02, 0.00) | | |
| >=85 | 409 | 1 | 0.2 | 415 | 2 | 0.5 | 0.5715 | 1.97 ( 0.18, 21.65) | 1.98 ( 0.18, 21.87) | 0.00 (-0.01, 0.01) | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.4473 |
| <30 | 161 | 2 | 1.2 | 148 | 3 | 2.0 | 0.5849 | 1.63 ( 0.28, | 9.63) | 1.64 ( 0.27, | 9.98) | 0.01 (-0.02, 0.04) | |
| 30 to <45 | 550 | 5 | 0.9 | 564 | 2 | 0.4 | 0.2416 | 0.39 ( 0.08, | 2.00) | 0.39 ( 0.07, | 2.01) | -0.01 (-0.01, 0.00) | |
| >=45 | 1289 | 15 | 1.2 | 1340 | 8 | 0.6 | 0.1188 | 0.51 ( 0.22, | 1.21) | 0.51 ( 0.22, | 1.21) | -0.01 (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.6754 |
| Normal (<30) | 764 | 4 | 0.5 | 787 | 4 | 0.5 | 0.9665 | 0.97 ( 0.24, | 3.87) | 0.97 ( 0.24, | 3.89) | 0.00 (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 7 | 0.8 | 938 | 4 | 0.4 | 0.3484 | 0.56 ( 0.16, | 1.91) | 0.56 ( 0.16, | 1.92) | 0.00 (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 311 | 11 | 3.5 | 318 | 5 | 1.6 | 0.1177 | 0.44 ( 0.16, | 1.26) | 0.44 ( 0.15, | 1.27) | -0.02 (-0.04, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.5953 |
| Low, moderate or high | 1477 | 15 | 1.0 | 1548 | 8 | 0.5 | 0.1144 | 0.51 ( 0.22, | 1.20) | 0.51 ( 0.21, | 1.20) | 0.00 (-0.01, 0.00) | |
| Very high | 519 | 7 | 1.3 | 495 | 5 | 1.0 | 0.6182 | 0.75 ( 0.24, | 2.34) | 0.75 ( 0.24, | 2.37) | 0.00 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.5527 |
| No | 411 | 2 | 0.5 | 410 | 2 | 0.5 | 0.9981 | 1.00 ( 0.14, | 7.08) | 1.00 ( 0.14, | 7.15) | 0.00 (-0.01, 0.01) | |
| Yes | 1590 | 20 | 1.3 | 1642 | 11 | 0.7 | 0.0864 | 0.53 ( 0.26, | 1.11) | 0.53 ( 0.25, | 1.11) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.2943 |
| No | 282 | 5 | 1.8 | 277 | 1 | 0.4 | 0.1053 | 0.20 ( 0.02, | 1.73) | 0.20 ( 0.02, | 1.73) | -0.01 (-0.03, 0.00) | |
| Yes | 1719 | 17 | 1.0 | 1775 | 12 | 0.7 | 0.3081 | 0.68 ( 0.33, | 1.43) | 0.68 ( 0.32, | 1.43) | 0.00 (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.2912 |
| No | 229 | 3 | 1.3 | 250 | 0 | 0 | 0.1106 | 0.13 (<0.01, | 2.52) | 0.13 (<0.01, | 2.51) | -0.01 (-0.03, 0.00) | |
| Yes | 1772 | 19 | 1.1 | 1802 | 13 | 0.7 | 0.2656 | 0.67 ( 0.33, | 1.36) | 0.67 ( 0.33, | 1.36) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 129 | 6.4 | 2052 | 91 | 4.4 | 0.0047 | 0.69 | ( 0.53, 0.89) | 0.67 | ( 0.51, 0.89) | -0.02 | (-0.03,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.7647 |
| Male | 1065 | 64 | 6.0 | 1093 | 47 | 4.3 | 0.0723 | 0.72 | ( 0.50, 1.03) | 0.70 | ( 0.48, 1.03) | -0.02 | (-0.04, 0.00) | |
| Female | 936 | 65 | 6.9 | 959 | 44 | 4.6 | 0.0276 | 0.66 | ( 0.46, 0.96) | 0.64 | ( 0.43, 0.96) | -0.02 | (-0.04, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.1384 |
| <65 | 331 | 23 | 6.9 | 313 | 22 | 7.0 | 0.9682 | 1.01 | ( 0.58, 1.78) | 1.01 | ( 0.55, 1.86) | 0.00 | (-0.04, 0.04) | |
| >=65 | 1670 | 106 | 6.3 | 1739 | 69 | 4.0 | 0.0016 | 0.63 | ( 0.47, 0.84) | 0.61 | ( 0.45, 0.83) | -0.02 | (-0.04,-0.01) | |
| Region | | | | | | | | | | | | | | 0.3032 |
| North America | 273 | 22 | 8.1 | 273 | 12 | 4.4 | 0.0766 | 0.55 | ( 0.28, 1.08) | 0.52 | ( 0.25, 1.08) | -0.04 | (-0.08, 0.00) | |
| Latin America | 511 | 26 | 5.1 | 504 | 27 | 5.4 | 0.8472 | 1.05 | ( 0.62, 1.78) | 1.06 | ( 0.61, 1.84) | 0.00 | (-0.02, 0.03) | |
| Europe | 865 | 45 | 5.2 | 894 | 25 | 2.8 | 0.0099 | 0.54 | ( 0.33, 0.87) | 0.52 | ( 0.32, 0.86) | -0.02 | (-0.04,-0.01) | |
| Asia | 231 | 29 | 12.6 | 248 | 19 | 7.7 | 0.0748 | 0.61 | ( 0.35, 1.06) | 0.58 | ( 0.31, 1.06) | -0.05 | (-0.10, 0.01) | |
| Other | 121 | 7 | 5.8 | 133 | 8 | 6.0 | 0.9381 | 1.04 | ( 0.39, 2.78) | 1.04 | ( 0.37, 2.97) | 0.00 | (-0.06, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6649 |
| Diabetic | 1045 | 68 | 6.5 | 1081 | 51 | 4.7 | 0.0728 | 0.73 | ( 0.51, 1.03) | 0.71 | ( 0.49, 1.03) | -0.02 | (-0.04, 0.00) | |
| Non-Diabetic | 956 | 61 | 6.4 | 971 | 40 | 4.1 | 0.0259 | 0.65 | ( 0.44, 0.95) | 0.63 | ( 0.42, 0.95) | -0.02 | (-0.04, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4053 |
| <30 | 1086 | 86 | 7.9 | 1094 | 55 | 5.0 | 0.0061 | 0.63 | ( 0.46, 0.88) | 0.62 | ( 0.43, 0.87) | -0.03 | (-0.05,-0.01) | |
| >=30 | 915 | 43 | 4.7 | 958 | 36 | 3.8 | 0.3108 | 0.80 | ( 0.52, 1.23) | 0.79 | ( 0.50, 1.24) | -0.01 | (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5051 |
| <130 | 827 | 62 | 7.5 | 853 | 48 | 5.6 | 0.1214 | 0.75 | ( 0.52, 1.08) | 0.74 | ( 0.50, 1.09) | -0.02 | (-0.04, 0.00) | |
| >=130 | 1174 | 67 | 5.7 | 1199 | 43 | 3.6 | 0.0140 | 0.63 | ( 0.43, 0.91) | 0.61 | ( 0.42, 0.91) | -0.02 | (-0.04, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8026 |
| <75 | 935 | 67 | 7.2 | 934 | 44 | 4.7 | 0.0248 | 0.66 | ( 0.45, 0.95) | 0.64 | ( 0.43, 0.95) | -0.02 | (-0.05, 0.00) | |
| 75 to <85 | 657 | 38 | 5.8 | 703 | 27 | 3.8 | 0.0932 | 0.66 | ( 0.41, 1.07) | 0.65 | ( 0.39, 1.08) | -0.02 | (-0.04, 0.00) | |
| >=85 | 409 | 24 | 5.9 | 415 | 20 | 4.8 | 0.5032 | 0.82 | ( 0.46, 1.46) | 0.81 | ( 0.44, 1.49) | -0.01 | (-0.04, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.5450 |
| <30 | 161 | 14 | 8.7 | 148 | 10 | 6.8 | 0.5247 | 0.78 ( 0.36, | 1.70) | 0.76 ( 0.33, | 1.77) | -0.02 (-0.08, 0.04) | |
| 30 to <45 | 550 | 35 | 6.4 | 564 | 19 | 3.4 | 0.0200 | 0.53 ( 0.31, | 0.91) | 0.51 ( 0.29, | 0.91) | -0.03 (-0.06, 0.00) | |
| >=45 | 1289 | 80 | 6.2 | 1340 | 62 | 4.6 | 0.0733 | 0.75 ( 0.54, | 1.03) | 0.73 ( 0.52, | 1.03) | -0.02 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.6587 |
| Normal (<30) | 764 | 46 | 6.0 | 787 | 28 | 3.6 | 0.0229 | 0.59 ( 0.37, | 0.94) | 0.58 ( 0.36, | 0.93) | -0.02 (-0.05, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 62 | 6.7 | 938 | 49 | 5.2 | 0.1701 | 0.78 ( 0.54, | 1.12) | 0.76 ( 0.52, | 1.12) | -0.02 (-0.04, 0.01) | |
| Macroalbuminuria (>300) | 311 | 20 | 6.4 | 318 | 14 | 4.4 | 0.2607 | 0.68 ( 0.35, | 1.33) | 0.67 ( 0.33, | 1.35) | -0.02 (-0.06, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.7358 |
| Low, moderate or high | 1477 | 93 | 6.3 | 1548 | 66 | 4.3 | 0.0123 | 0.68 ( 0.50, | 0.92) | 0.66 ( 0.48, | 0.92) | -0.02 (-0.04, 0.00) | |
| Very high | 519 | 35 | 6.7 | 495 | 25 | 5.1 | 0.2533 | 0.75 ( 0.46, | 1.23) | 0.74 ( 0.43, | 1.25) | -0.02 (-0.05, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.9425 |
| No | 411 | 34 | 8.3 | 410 | 23 | 5.6 | 0.1334 | 0.68 ( 0.41, | 1.13) | 0.66 ( 0.38, | 1.14) | -0.03 (-0.06, 0.01) | |
| Yes | 1590 | 95 | 6.0 | 1642 | 68 | 4.1 | 0.0172 | 0.69 ( 0.51, | 0.94) | 0.68 ( 0.49, | 0.94) | -0.02 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.2910 |
| No | 282 | 23 | 8.2 | 277 | 11 | 4.0 | 0.0385 | 0.49 ( 0.24, | 0.98) | 0.47 ( 0.22, | 0.97) | -0.04 (-0.08, 0.00) | |
| Yes | 1719 | 106 | 6.2 | 1775 | 80 | 4.5 | 0.0289 | 0.73 ( 0.55, | 0.97) | 0.72 ( 0.53, | 0.97) | -0.02 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.0728 |
| No | 229 | 12 | 5.2 | 250 | 3 | 1.2 | 0.0112 | 0.23 ( 0.07, | 0.80) | 0.22 ( 0.06, | 0.79) | -0.04 (-0.07,-0.01) | |
| Yes | 1772 | 117 | 6.6 | 1802 | 88 | 4.9 | 0.0271 | 0.74 ( 0.57, | 0.97) | 0.73 ( 0.55, | 0.97) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 5 | 0.2 | 2052 | 6 | 0.3 | 0.7947 | 1.17 ( 0.36, 3.83) | 1.17 ( 0.36, 3.84) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 1065 | 2 | 0.2 | 1093 | 3 | 0.3 | | | | | |
| Female | 936 | 3 | 0.3 | 959 | 3 | 0.3 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 331 | 5 | 1.5 | 313 | 1 | 0.3 | | | | | |
| >=65 | 1670 | 0 | 0 | 1739 | 5 | 0.3 | | | | | |
| Region | | | | | | | | | | | |
| North America | 273 | 1 | 0.4 | 273 | 3 | 1.1 | | | | | |
| Latin America | 511 | 1 | 0.2 | 504 | 0 | 0 | | | | | |
| Europe | 865 | 0 | 0 | 894 | 1 | 0.1 | | | | | |
| Asia | 231 | 1 | 0.4 | 248 | 0 | 0 | | | | | |
| Other | 121 | 2 | 1.7 | 133 | 2 | 1.5 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | 0.9374 |
| Diabetic | 1045 | 5 | 0.5 | 1081 | 6 | 0.6 | 0.8057 | 1.16 ( 0.36, 3.79) | 1.16 ( 0.35, 3.82) | 0.00 (-0.01, 0.01) | |
| Non-Diabetic | 956 | 0 | 0 | 971 | 0 | 0 | 0.9938 | 0.98 ( 0.02, 49.57) | 0.98 ( 0.02, 49.67) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 1086 | 2 | 0.2 | 1094 | 2 | 0.2 | | | | | |
| >=30 | 915 | 3 | 0.3 | 958 | 4 | 0.4 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 827 | 2 | 0.2 | 853 | 1 | 0.1 | | | | | |
| >=130 | 1174 | 3 | 0.3 | 1199 | 5 | 0.4 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 935 | 1 | 0.1 | 934 | 3 | 0.3 | | | | | |
| 75 to <85 | 657 | 2 | 0.3 | 703 | 3 | 0.4 | | | | | |
| >=85 | 409 | 2 | 0.5 | 415 | 0 | 0 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 161 | 2 | 1.2 | 148 | 1 | 0.7 | | | | | |
| 30 to <45 | 550 | 1 | 0.2 | 564 | 2 | 0.4 | | | | | |
| >=45 | 1289 | 2 | 0.2 | 1340 | 3 | 0.2 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 764 | 1 | 0.1 | 787 | 1 | 0.1 | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 3 | 0.3 | 938 | 2 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 311 | 1 | 0.3 | 318 | 3 | 0.9 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1477 | 3 | 0.2 | 1548 | 4 | 0.3 | | | | | |
| Very high | 519 | 2 | 0.4 | 495 | 2 | 0.4 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 411 | 2 | 0.5 | 410 | 1 | 0.2 | | | | | |
| Yes | 1590 | 3 | 0.2 | 1642 | 5 | 0.3 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 282 | 0 | 0 | 277 | 2 | 0.7 | | | | | |
| Yes | 1719 | 5 | 0.3 | 1775 | 4 | 0.2 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 229 | 1 | 0.4 | 250 | 2 | 0.8 | | | | | |
| Yes | 1772 | 4 | 0.2 | 1802 | 4 | 0.2 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 84 | 4.2 | 2052 | 84 | 4.1 | 0.8677 | 0.98 ( 0.73, | 1.31) | 0.97 ( 0.72, | 1.33) | 0.00 (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | 0.5312 |
| Male | 1065 | 43 | 4.0 | 1093 | 47 | 4.3 | 0.7604 | 1.07 ( 0.71, | 1.60) | 1.07 ( 0.70, | 1.63) | 0.00 (-0.01, 0.02) | |
| Female | 936 | 41 | 4.4 | 959 | 37 | 3.9 | 0.5673 | 0.88 ( 0.57, | 1.36) | 0.88 ( 0.56, | 1.38) | -0.01 (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | 0.5150 |
| <65 | 331 | 16 | 4.8 | 313 | 18 | 5.8 | 0.6030 | 1.19 ( 0.62, | 2.29) | 1.20 ( 0.60, | 2.40) | 0.01 (-0.03, 0.04) | |
| >=65 | 1670 | 68 | 4.1 | 1739 | 66 | 3.8 | 0.6778 | 0.93 ( 0.67, | 1.30) | 0.93 ( 0.66, | 1.31) | 0.00 (-0.02, 0.01) | |
| Region | | | | | | | | | | | | | 0.8612 |
| North America | 273 | 14 | 5.1 | 273 | 19 | 7.0 | 0.3692 | 1.36 ( 0.69, | 2.65) | 1.38 ( 0.68, | 2.82) | 0.02 (-0.02, 0.06) | |
| Latin America | 511 | 31 | 6.1 | 504 | 26 | 5.2 | 0.5299 | 0.85 ( 0.51, | 1.41) | 0.84 ( 0.49, | 1.44) | -0.01 (-0.04, 0.02) | |
| Europe | 865 | 26 | 3.0 | 894 | 25 | 2.8 | 0.7936 | 0.93 ( 0.54, | 1.60) | 0.93 ( 0.53, | 1.62) | 0.00 (-0.02, 0.01) | |
| Asia | 231 | 6 | 2.6 | 248 | 7 | 2.8 | 0.8795 | 1.09 ( 0.37, | 3.19) | 1.09 ( 0.36, | 3.29) | 0.00 (-0.03, 0.03) | |
| Other | 121 | 7 | 5.8 | 133 | 7 | 5.3 | 0.8555 | 0.91 ( 0.33, | 2.52) | 0.90 ( 0.31, | 2.66) | -0.01 (-0.06, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.7475 |
| Diabetic | 1045 | 78 | 7.5 | 1081 | 77 | 7.1 | 0.7623 | 0.95 ( 0.70, | 1.29) | 0.95 ( 0.69, | 1.32) | 0.00 (-0.03, 0.02) | |
| Non-Diabetic | 956 | 6 | 0.6 | 971 | 7 | 0.7 | 0.8025 | 1.15 ( 0.39, | 3.41) | 1.15 ( 0.38, | 3.43) | 0.00 (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.2576 |
| <30 | 1086 | 45 | 4.1 | 1094 | 37 | 3.4 | 0.3501 | 0.82 ( 0.53, | 1.25) | 0.81 ( 0.52, | 1.26) | -0.01 (-0.02, 0.01) | |
| >=30 | 915 | 39 | 4.3 | 958 | 47 | 4.9 | 0.5058 | 1.15 ( 0.76, | 1.74) | 1.16 ( 0.75, | 1.79) | 0.01 (-0.01, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.9750 |
| <130 | 827 | 30 | 3.6 | 853 | 30 | 3.5 | 0.9028 | 0.97 ( 0.59, | 1.59) | 0.97 ( 0.58, | 1.62) | 0.00 (-0.02, 0.02) | |
| >=130 | 1174 | 54 | 4.6 | 1199 | 54 | 4.5 | 0.9108 | 0.98 ( 0.68, | 1.42) | 0.98 ( 0.66, | 1.44) | 0.00 (-0.02, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.3400 |
| <75 | 935 | 50 | 5.3 | 934 | 40 | 4.3 | 0.2823 | 0.80 ( 0.53, | 1.20) | 0.79 ( 0.52, | 1.21) | -0.01 (-0.03, 0.01) | |
| 75 to <85 | 657 | 19 | 2.9 | 703 | 27 | 3.8 | 0.3335 | 1.33 ( 0.75, | 2.37) | 1.34 ( 0.74, | 2.44) | 0.01 (-0.01, 0.03) | |
| >=85 | 409 | 15 | 3.7 | 415 | 17 | 4.1 | 0.7500 | 1.12 ( 0.57, | 2.21) | 1.12 ( 0.55, | 2.28) | 0.00 (-0.02, 0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.4186 |
| <30 | 161 | 15 | 9.3 | 148 | 20 | 13.5 | 0.2449 | 1.45 ( 0.77, 2.73) | 1.52 ( 0.75, 3.09) | 0.04 (-0.03, 0.11) | |
| 30 to <45 | 550 | 26 | 4.7 | 564 | 24 | 4.3 | 0.7037 | 0.90 ( 0.52, 1.55) | 0.90 ( 0.51, 1.58) | 0.00 (-0.03, 0.02) | |
| >=45 | 1289 | 43 | 3.3 | 1340 | 40 | 3.0 | 0.6070 | 0.89 ( 0.59, 1.37) | 0.89 ( 0.58, 1.38) | 0.00 (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.7141 |
| Normal (<30) | 764 | 20 | 2.6 | 787 | 18 | 2.3 | 0.6737 | 0.87 ( 0.47, 1.64) | 0.87 ( 0.46, 1.66) | 0.00 (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 34 | 3.7 | 938 | 39 | 4.2 | 0.6049 | 1.13 ( 0.72, 1.77) | 1.13 ( 0.71, 1.81) | 0.00 (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 311 | 30 | 9.6 | 318 | 27 | 8.5 | 0.6137 | 0.88 ( 0.54, 1.45) | 0.87 ( 0.50, 1.50) | -0.01 (-0.06, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.7535 |
| Low, moderate or high | 1477 | 40 | 2.7 | 1548 | 40 | 2.6 | 0.8315 | 0.95 ( 0.62, 1.47) | 0.95 ( 0.61, 1.49) | 0.00 (-0.01, 0.01) | |
| Very high | 519 | 44 | 8.5 | 495 | 44 | 8.9 | 0.8162 | 1.05 ( 0.70, 1.56) | 1.05 ( 0.68, 1.63) | 0.00 (-0.03, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.6147 |
| No | 411 | 18 | 4.4 | 410 | 15 | 3.7 | 0.5989 | 0.84 ( 0.43, 1.63) | 0.83 ( 0.41, 1.67) | -0.01 (-0.03, 0.02) | |
| Yes | 1590 | 66 | 4.2 | 1642 | 69 | 4.2 | 0.9420 | 1.01 ( 0.73, 1.41) | 1.01 ( 0.72, 1.43) | 0.00 (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.9277 |
| No | 282 | 7 | 2.5 | 277 | 7 | 2.5 | 0.9730 | 1.02 ( 0.36, 2.86) | 1.02 ( 0.35, 2.94) | 0.00 (-0.03, 0.03) | |
| Yes | 1719 | 77 | 4.5 | 1775 | 77 | 4.3 | 0.8388 | 0.97 ( 0.71, 1.32) | 0.97 ( 0.70, 1.34) | 0.00 (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.1701 |
| No | 229 | 12 | 5.2 | 250 | 7 | 2.8 | 0.1717 | 0.53 ( 0.21, 1.33) | 0.52 ( 0.20, 1.35) | -0.02 (-0.06, 0.01) | |
| Yes | 1772 | 72 | 4.1 | 1802 | 77 | 4.3 | 0.7537 | 1.05 ( 0.77, 1.44) | 1.05 ( 0.76, 1.46) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 206 | 10.3 | 2052 | 257 | 12.5 | 0.0257 | 1.22 | ( 1.02, 1.45) | 1.25 | ( 1.03, 1.52) | 0.02 | ( 0.00, 0.04) | |
| Sex | | | | | | | | | | | | | | 0.3438 |
| Male | 1065 | 73 | 6.9 | 1093 | 81 | 7.4 | 0.6157 | 1.08 | ( 0.80, 1.47) | 1.09 | ( 0.78, 1.51) | 0.01 | (-0.02, 0.03) | |
| Female | 936 | 133 | 14.2 | 959 | 176 | 18.4 | 0.0147 | 1.29 | ( 1.05, 1.59) | 1.36 | ( 1.06, 1.74) | 0.04 | ( 0.01, 0.07) | |
| Age [years] | | | | | | | | | | | | | | 0.1651 |
| <65 | 331 | 21 | 6.3 | 313 | 34 | 10.9 | 0.0403 | 1.71 | ( 1.02, 2.88) | 1.80 | ( 1.02, 3.17) | 0.05 | ( 0.00, 0.09) | |
| >=65 | 1670 | 185 | 11.1 | 1739 | 223 | 12.8 | 0.1165 | 1.16 | ( 0.96, 1.39) | 1.18 | ( 0.96, 1.45) | 0.02 | ( 0.00, 0.04) | |
| Region | | | | | | | | | | | | | | 0.0947 |
| North America | 273 | 44 | 16.1 | 273 | 43 | 15.8 | 0.9069 | 0.98 | ( 0.66, 1.44) | 0.97 | ( 0.62, 1.54) | 0.00 | (-0.07, 0.06) | |
| Latin America | 511 | 46 | 9.0 | 504 | 73 | 14.5 | 0.0066 | 1.61 | ( 1.14, 2.28) | 1.71 | ( 1.16, 2.53) | 0.05 | ( 0.02, 0.09) | |
| Europe | 865 | 87 | 10.1 | 894 | 95 | 10.6 | 0.6955 | 1.06 | ( 0.80, 1.39) | 1.06 | ( 0.78, 1.45) | 0.01 | (-0.02, 0.03) | |
| Asia | 231 | 14 | 6.1 | 248 | 14 | 5.6 | 0.8464 | 0.93 | ( 0.45, 1.91) | 0.93 | ( 0.43, 1.99) | 0.00 | (-0.05, 0.04) | |
| Other | 121 | 15 | 12.4 | 133 | 32 | 24.1 | 0.0168 | 1.94 | ( 1.11, 3.40) | 2.24 | ( 1.14, 4.38) | 0.12 | ( 0.02, 0.21) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3577 |
| Diabetic | 1045 | 114 | 10.9 | 1081 | 133 | 12.3 | 0.3159 | 1.13 | ( 0.89, 1.43) | 1.15 | ( 0.88, 1.49) | 0.01 | (-0.01, 0.04) | |
| Non-Diabetic | 956 | 92 | 9.6 | 971 | 124 | 12.8 | 0.0286 | 1.33 | ( 1.03, 1.71) | 1.37 | ( 1.03, 1.83) | 0.03 | ( 0.00, 0.06) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4009 |
| <30 | 1086 | 109 | 10.0 | 1094 | 124 | 11.3 | 0.3268 | 1.13 | ( 0.89, 1.44) | 1.15 | ( 0.87, 1.50) | 0.01 | (-0.01, 0.04) | |
| >=30 | 915 | 97 | 10.6 | 958 | 133 | 13.9 | 0.0305 | 1.31 | ( 1.02, 1.67) | 1.36 | ( 1.03, 1.80) | 0.03 | ( 0.00, 0.06) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3220 |
| <130 | 827 | 82 | 9.9 | 853 | 114 | 13.4 | 0.0277 | 1.35 | ( 1.03, 1.76) | 1.40 | ( 1.04, 1.89) | 0.03 | ( 0.00, 0.07) | |
| >=130 | 1174 | 124 | 10.6 | 1199 | 143 | 11.9 | 0.2930 | 1.13 | ( 0.90, 1.42) | 1.15 | ( 0.89, 1.48) | 0.01 | (-0.01, 0.04) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7209 |
| <75 | 935 | 109 | 11.7 | 934 | 130 | 13.9 | 0.1434 | 1.19 | ( 0.94, 1.51) | 1.23 | ( 0.93, 1.61) | 0.02 | (-0.01, 0.05) | |
| 75 to <85 | 657 | 63 | 9.6 | 703 | 78 | 11.1 | 0.3625 | 1.16 | ( 0.84, 1.58) | 1.18 | ( 0.83, 1.67) | 0.02 | (-0.02, 0.05) | |
| >=85 | 409 | 34 | 8.3 | 415 | 49 | 11.8 | 0.0957 | 1.42 | ( 0.94, 2.15) | 1.48 | ( 0.93, 2.34) | 0.03 | (-0.01, 0.08) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.1315 |
| <30 | 161 | 28 | 17.4 | 148 | 23 | 15.5 | 0.6615 | 0.89 ( 0.54, | 1.48) | 0.87 ( 0.48, | 1.60) | -0.02 (-0.10, 0.06) | |
| 30 to <45 | 550 | 74 | 13.5 | 564 | 80 | 14.2 | 0.7242 | 1.05 ( 0.79, | 1.41) | 1.06 ( 0.76, | 1.49) | 0.01 (-0.03, 0.05) | |
| >=45 | 1289 | 104 | 8.1 | 1340 | 154 | 11.5 | 0.0032 | 1.42 ( 1.12, | 1.80) | 1.48 ( 1.14, | 1.92) | 0.03 ( 0.01, 0.06) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.9001 |
| Normal (<30) | 764 | 81 | 10.6 | 787 | 98 | 12.5 | 0.2542 | 1.17 ( 0.89, | 1.55) | 1.20 ( 0.88, | 1.64) | 0.02 (-0.01, 0.05) | |
| Microalbuminuria (30 to <=300) | 921 | 96 | 10.4 | 938 | 121 | 12.9 | 0.0964 | 1.24 ( 0.96, | 1.59) | 1.27 ( 0.96, | 1.69) | 0.02 ( 0.00, 0.05) | |
| Macroalbuminuria (>300) | 311 | 28 | 9.0 | 318 | 38 | 11.9 | 0.2280 | 1.33 ( 0.84, | 2.11) | 1.37 ( 0.82, | 2.30) | 0.03 (-0.02, 0.08) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.1662 |
| Low, moderate or high | 1477 | 131 | 8.9 | 1548 | 184 | 11.9 | 0.0066 | 1.34 ( 1.08, | 1.66) | 1.39 ( 1.09, | 1.76) | 0.03 ( 0.01, 0.05) | |
| Very high | 519 | 74 | 14.3 | 495 | 73 | 14.7 | 0.8249 | 1.03 ( 0.77, | 1.39) | 1.04 ( 0.73, | 1.48) | 0.00 (-0.04, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.6215 |
| No | 411 | 48 | 11.7 | 410 | 63 | 15.4 | 0.1224 | 1.32 ( 0.93, | 1.87) | 1.37 ( 0.92, | 2.06) | 0.04 (-0.01, 0.08) | |
| Yes | 1590 | 158 | 9.9 | 1642 | 194 | 11.8 | 0.0867 | 1.19 ( 0.98, | 1.45) | 1.21 ( 0.97, | 1.52) | 0.02 ( 0.00, 0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.7168 |
| No | 282 | 27 | 9.6 | 277 | 35 | 12.6 | 0.2492 | 1.32 ( 0.82, | 2.12) | 1.37 ( 0.80, | 2.33) | 0.03 (-0.02, 0.08) | |
| Yes | 1719 | 179 | 10.4 | 1775 | 222 | 12.5 | 0.0522 | 1.20 (<1.00, | 1.45) | 1.23 ( 1.00, | 1.52) | 0.02 ( 0.00, 0.04) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.2673 |
| No | 229 | 20 | 8.7 | 250 | 35 | 14.0 | 0.0709 | 1.60 ( 0.95, | 2.69) | 1.70 ( 0.95, | 3.04) | 0.05 ( 0.00, 0.11) | |
| Yes | 1772 | 186 | 10.5 | 1802 | 222 | 12.3 | 0.0866 | 1.17 ( 0.98, | 1.41) | 1.20 ( 0.97, | 1.47) | 0.02 ( 0.00, 0.04) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 2001 | 20 | 1.0 | 2052 | 48 | 2.3 | 0.0009 | 2.34 ( 1.39, 3.93) | 2.37 ( 1.40, 4.01) | 0.01 ( 0.01, 0.02) | | |
| Sex | | | | | | | | | | | | 0.5282 |
| Male | 1065 | 10 | 0.9 | 1093 | 28 | 2.6 | 0.0042 | 2.73 ( 1.33, 5.59) | 2.77 ( 1.34, 5.74) | 0.02 ( 0.01, 0.03) | | |
| Female | 936 | 10 | 1.1 | 959 | 20 | 2.1 | 0.0761 | 1.95 ( 0.92, 4.15) | 1.97 ( 0.92, 4.24) | 0.01 ( 0.00, 0.02) | | |
| Age [years] | | | | | | | | | | | | 0.2629 |
| <65 | 331 | 5 | 1.5 | 313 | 6 | 1.9 | 0.6908 | 1.27 ( 0.39, 4.12) | 1.27 ( 0.38, 4.22) | 0.00 (-0.02, 0.02) | | |
| >=65 | 1670 | 15 | 0.9 | 1739 | 42 | 2.4 | 0.0006 | 2.69 ( 1.50, 4.83) | 2.73 ( 1.51, 4.94) | 0.02 ( 0.01, 0.02) | | |
| Region | | | | | | | | | | | | 0.2632 |
| North America | 273 | 7 | 2.6 | 273 | 15 | 5.5 | 0.0817 | 2.14 ( 0.89, 5.17) | 2.21 ( 0.89, 5.51) | 0.03 ( 0.00, 0.06) | | |
| Latin America | 511 | 4 | 0.8 | 504 | 9 | 1.8 | 0.1554 | 2.28 ( 0.71, 7.36) | 2.30 ( 0.71, 7.53) | 0.01 ( 0.00, 0.02) | | |
| Europe | 865 | 4 | 0.5 | 894 | 20 | 2.2 | 0.0013 | 4.84 ( 1.66, 14.10) | 4.93 ( 1.68, 14.47) | 0.02 ( 0.01, 0.03) | | |
| Asia | 231 | 2 | 0.9 | 248 | 0 | 0 | 0.2223 | 0.19 (<0.01, 3.86) | 0.18 (<0.01, 3.87) | -0.01 (-0.02, 0.01) | | |
| Other | 121 | 3 | 2.5 | 133 | 4 | 3.0 | 0.7973 | 1.21 ( 0.28, 5.31) | 1.22 ( 0.27, 5.56) | 0.01 (-0.03, 0.05) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1563 |
| Diabetic | 1045 | 16 | 1.5 | 1081 | 30 | 2.8 | 0.0487 | 1.81 ( 0.99, 3.31) | 1.84 ( 0.99, 3.39) | 0.01 ( 0.00, 0.02) | | |
| Non-Diabetic | 956 | 4 | 0.4 | 971 | 18 | 1.9 | 0.0030 | 4.43 ( 1.50, 13.04) | 4.50 ( 1.52, 13.33) | 0.01 ( 0.00, 0.02) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.6697 |
| <30 | 1086 | 7 | 0.6 | 1094 | 19 | 1.7 | 0.0188 | 2.69 ( 1.14, 6.38) | 2.72 ( 1.14, 6.51) | 0.01 ( 0.00, 0.02) | | |
| >=30 | 915 | 13 | 1.4 | 958 | 29 | 3.0 | 0.0189 | 2.13 ( 1.11, 4.07) | 2.17 ( 1.12, 4.19) | 0.02 ( 0.00, 0.03) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8396 |
| <130 | 827 | 9 | 1.1 | 853 | 23 | 2.7 | 0.0159 | 2.48 ( 1.15, 5.32) | 2.52 ( 1.16, 5.48) | 0.02 ( 0.00, 0.03) | | |
| >=130 | 1174 | 11 | 0.9 | 1199 | 25 | 2.1 | 0.0222 | 2.23 ( 1.10, 4.50) | 2.25 ( 1.10, 4.60) | 0.01 ( 0.00, 0.02) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3819 |
| <75 | 935 | 11 | 1.2 | 934 | 20 | 2.1 | 0.1025 | 1.82 ( 0.88, 3.78) | 1.84 ( 0.88, 3.86) | 0.01 ( 0.00, 0.02) | | |
| 75 to <85 | 657 | 6 | 0.9 | 703 | 13 | 1.8 | 0.1417 | 2.02 ( 0.77, 5.30) | 2.04 ( 0.77, 5.41) | 0.01 ( 0.00, 0.02) | | |
| >=85 | 409 | 3 | 0.7 | 415 | 15 | 3.6 | 0.0047 | 4.93 ( 1.44, 16.89) | 5.08 ( 1.46, 17.66) | 0.03 ( 0.01, 0.05) | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.8316 |
| <30 | 161 | 2 | 1.2 | 148 | 3 | 2.0 | 0.5849 | 1.63 ( 0.28, 9.63) | 1.64 ( 0.27, 9.98) | 0.01 (-0.02, 0.04) | |
| 30 to <45 | 550 | 5 | 0.9 | 564 | 10 | 1.8 | 0.2110 | 1.95 ( 0.67, 5.67) | 1.97 ( 0.67, 5.79) | 0.01 ( 0.00, 0.02) | |
| >=45 | 1289 | 13 | 1.0 | 1340 | 35 | 2.6 | 0.0021 | 2.59 ( 1.38, 4.87) | 2.63 ( 1.39, 5.00) | 0.02 ( 0.01, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.8726 |
| Normal (<30) | 764 | 6 | 0.8 | 787 | 17 | 2.2 | 0.0251 | 2.75 ( 1.09, 6.94) | 2.79 ( 1.09, 7.11) | 0.01 ( 0.00, 0.03) | |
| Microalbuminuria (30 to <=300) | 921 | 11 | 1.2 | 938 | 23 | 2.5 | 0.0430 | 2.05 ( 1.01, 4.19) | 2.08 ( 1.01, 4.29) | 0.01 ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 311 | 3 | 1.0 | 318 | 8 | 2.5 | 0.1379 | 2.61 ( 0.70, 9.74) | 2.65 ( 0.70, 10.08) | 0.02 ( 0.00, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.5161 |
| Low, moderate or high | 1477 | 15 | 1.0 | 1548 | 40 | 2.6 | 0.0012 | 2.54 ( 1.41, 4.59) | 2.59 ( 1.42, 4.70) | 0.02 ( 0.01, 0.03) | |
| Very high | 519 | 5 | 1.0 | 495 | 8 | 1.6 | 0.3557 | 1.68 ( 0.55, 5.09) | 1.69 ( 0.55, 5.20) | 0.01 (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3358 |
| No | 411 | 6 | 1.5 | 410 | 9 | 2.2 | 0.4316 | 1.50 ( 0.54, 4.19) | 1.51 ( 0.53, 4.30) | 0.01 (-0.01, 0.03) | |
| Yes | 1590 | 14 | 0.9 | 1642 | 39 | 2.4 | 0.0008 | 2.70 ( 1.47, 4.95) | 2.74 ( 1.48, 5.06) | 0.01 ( 0.01, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.2617 |
| No | 282 | 0 | 0 | 277 | 5 | 1.8 | 0.0381 | 11.20 ( 0.62,201.55) | 11.40 ( 0.63,207.22) | 0.02 ( 0.00, 0.04) | |
| Yes | 1719 | 20 | 1.2 | 1775 | 43 | 2.4 | 0.0052 | 2.08 ( 1.23, 3.52) | 2.11 ( 1.24, 3.60) | 0.01 ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.6711 |
| No | 229 | 2 | 0.9 | 250 | 7 | 2.8 | 0.1208 | 3.21 ( 0.67, 15.28) | 3.27 ( 0.67, 15.90) | 0.02 ( 0.00, 0.04) | |
| Yes | 1772 | 18 | 1.0 | 1802 | 41 | 2.3 | 0.0031 | 2.24 ( 1.29, 3.88) | 2.27 ( 1.30, 3.96) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 2001 | 16 | 0.8 | 2052 | 26 | 1.3 | 0.1418 | 1.58 ( 0.85, 2.94) | 1.59 ( 0.85, 2.98) | 0.00 ( 0.00, 0.01) | | |
| Sex | | | | | | | | | | | | 0.3777 |
| Male | 1065 | 9 | 0.8 | 1093 | 11 | 1.0 | 0.6958 | 1.19 ( 0.50, 2.86) | 1.19 ( 0.49, 2.89) | 0.00 (-0.01, 0.01) | | |
| Female | 936 | 7 | 0.7 | 959 | 15 | 1.6 | 0.0972 | 2.09 ( 0.86, 5.11) | 2.11 ( 0.86, 5.20) | 0.01 ( 0.00, 0.02) | | |
| Age [years] | | | | | | | | | | | | 0.7749 |
| <65 | 331 | 1 | 0.3 | 313 | 1 | 0.3 | 0.9684 | 1.06 ( 0.07, 16.83) | 1.06 ( 0.07, 16.98) | 0.00 (-0.01, 0.01) | | |
| >=65 | 1670 | 15 | 0.9 | 1739 | 25 | 1.4 | 0.1437 | 1.60 ( 0.85, 3.03) | 1.61 ( 0.85, 3.06) | 0.01 ( 0.00, 0.01) | | |
| Region | | | | | | | | | | | | 0.7281 |
| North America | 273 | 2 | 0.7 | 273 | 4 | 1.5 | 0.4116 | 2.00 ( 0.37, 10.83) | 2.01 ( 0.37, 11.09) | 0.01 (-0.01, 0.02) | | |
| Latin America | 511 | 3 | 0.6 | 504 | 5 | 1.0 | 0.4657 | 1.69 ( 0.41, 7.03) | 1.70 ( 0.40, 7.14) | 0.00 (-0.01, 0.01) | | |
| Europe | 865 | 8 | 0.9 | 894 | 8 | 0.9 | 0.9472 | 0.97 ( 0.36, 2.57) | 0.97 ( 0.36, 2.59) | 0.00 (-0.01, 0.01) | | |
| Asia | 231 | 1 | 0.4 | 248 | 5 | 2.0 | 0.1195 | 4.66 ( 0.55, 39.57) | 4.73 ( 0.55, 40.81) | 0.02 ( 0.00, 0.04) | | |
| Other | 121 | 2 | 1.7 | 133 | 4 | 3.0 | 0.4777 | 1.82 ( 0.34, 9.76) | 1.84 ( 0.33, 10.26) | 0.01 (-0.02, 0.05) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.4798 |
| Diabetic | 1045 | 8 | 0.8 | 1081 | 16 | 1.5 | 0.1190 | 1.93 ( 0.83, 4.50) | 1.95 ( 0.83, 4.57) | 0.01 ( 0.00, 0.02) | | |
| Non-Diabetic | 956 | 8 | 0.8 | 971 | 10 | 1.0 | 0.6596 | 1.23 ( 0.49, 3.10) | 1.23 ( 0.48, 3.14) | 0.00 (-0.01, 0.01) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0291 |
| <30 | 1086 | 12 | 1.1 | 1094 | 10 | 0.9 | 0.6557 | 0.83 ( 0.36, 1.91) | 0.83 ( 0.36, 1.92) | 0.00 (-0.01, 0.01) | | |
| >=30 | 915 | 4 | 0.4 | 958 | 16 | 1.7 | 0.0095 | 3.82 ( 1.28, 11.38) | 3.87 ( 1.29, 11.61) | 0.01 ( 0.00, 0.02) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5138 |
| <130 | 827 | 9 | 1.1 | 853 | 12 | 1.4 | 0.5569 | 1.29 ( 0.55, 3.05) | 1.30 ( 0.54, 3.09) | 0.00 (-0.01, 0.01) | | |
| >=130 | 1174 | 7 | 0.6 | 1199 | 14 | 1.2 | 0.1373 | 1.96 ( 0.79, 4.83) | 1.97 ( 0.79, 4.90) | 0.01 ( 0.00, 0.01) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4715 |
| <75 | 935 | 8 | 0.9 | 934 | 8 | 0.9 | 0.9983 | 1.00 ( 0.38, 2.66) | 1.00 ( 0.37, 2.68) | 0.00 (-0.01, 0.01) | | |
| 75 to <85 | 657 | 5 | 0.8 | 703 | 10 | 1.4 | 0.2432 | 1.87 ( 0.64, 5.44) | 1.88 ( 0.64, 5.53) | 0.01 ( 0.00, 0.02) | | |
| >=85 | 409 | 3 | 0.7 | 415 | 8 | 1.9 | 0.1353 | 2.63 ( 0.70, 9.84) | 2.66 ( 0.70, 10.10) | 0.01 ( 0.00, 0.03) | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.8073 |
| <30 | 161 | 4 | 2.5 | 148 | 4 | 2.7 | 0.9039 | 1.09 ( 0.28, 4.27) | 1.09 ( 0.27, 4.44) | 0.00 (-0.03, 0.04) | |
| 30 to <45 | 550 | 7 | 1.3 | 564 | 12 | 2.1 | 0.2705 | 1.67 ( 0.66, 4.21) | 1.69 ( 0.66, 4.32) | 0.01 (-0.01, 0.02) | |
| >=45 | 1289 | 5 | 0.4 | 1340 | 10 | 0.7 | 0.2226 | 1.92 ( 0.66, 5.61) | 1.93 ( 0.66, 5.66) | 0.00 ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.9436 |
| Normal (<30) | 764 | 6 | 0.8 | 787 | 11 | 1.4 | 0.2469 | 1.78 ( 0.66, 4.79) | 1.79 ( 0.66, 4.87) | 0.01 ( 0.00, 0.02) | |
| Microalbuminuria (30 to <=300) | 921 | 7 | 0.8 | 938 | 10 | 1.1 | 0.4882 | 1.40 ( 0.54, 3.67) | 1.41 ( 0.53, 3.71) | 0.00 (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 311 | 3 | 1.0 | 318 | 5 | 1.6 | 0.4965 | 1.63 ( 0.39, 6.76) | 1.64 ( 0.39, 6.92) | 0.01 (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8045 |
| Low, moderate or high | 1477 | 7 | 0.5 | 1548 | 13 | 0.8 | 0.2146 | 1.77 ( 0.71, 4.43) | 1.78 ( 0.71, 4.47) | 0.00 ( 0.00, 0.01) | |
| Very high | 519 | 9 | 1.7 | 495 | 13 | 2.6 | 0.3297 | 1.51 ( 0.65, 3.51) | 1.53 ( 0.65, 3.61) | 0.01 (-0.01, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.2602 |
| No | 411 | 2 | 0.5 | 410 | 7 | 1.7 | 0.0930 | 3.51 ( 0.73, 16.79) | 3.55 ( 0.73, 17.20) | 0.01 ( 0.00, 0.03) | |
| Yes | 1590 | 14 | 0.9 | 1642 | 19 | 1.2 | 0.4342 | 1.31 ( 0.66, 2.61) | 1.32 ( 0.66, 2.64) | 0.00 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.3699 |
| No | 282 | 2 | 0.7 | 277 | 6 | 2.2 | 0.1471 | 3.05 ( 0.62, 15.00) | 3.10 ( 0.62, 15.49) | 0.01 (-0.01, 0.03) | |
| Yes | 1719 | 14 | 0.8 | 1775 | 20 | 1.1 | 0.3471 | 1.38 ( 0.70, 2.73) | 1.39 ( 0.70, 2.76) | 0.00 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.2883 |
| No | 229 | 2 | 0.9 | 250 | 1 | 0.4 | 0.5118 | 0.46 ( 0.04, 5.02) | 0.46 ( 0.04, 5.06) | 0.00 (-0.02, 0.01) | |
| Yes | 1772 | 14 | 0.8 | 1802 | 25 | 1.4 | 0.0857 | 1.76 ( 0.92, 3.37) | 1.77 ( 0.92, 3.41) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 110 | 5.5 | 2052 | 121 | 5.9 | 0.5834 | 1.07 | ( 0.83, 1.38) | 1.08 | ( 0.83, 1.41) | 0.00 | (-0.01, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.4623 |
| Male | 1065 | 45 | 4.2 | 1093 | 44 | 4.0 | 0.8155 | 0.95 | ( 0.63, 1.43) | 0.95 | ( 0.62, 1.45) | 0.00 | (-0.02, 0.01) | |
| Female | 936 | 65 | 6.9 | 959 | 77 | 8.0 | 0.3699 | 1.16 | ( 0.84, 1.59) | 1.17 | ( 0.83, 1.65) | 0.01 | (-0.01, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.8012 |
| <65 | 331 | 11 | 3.3 | 313 | 10 | 3.2 | 0.9270 | 0.96 | ( 0.41, 2.23) | 0.96 | ( 0.40, 2.29) | 0.00 | (-0.03, 0.03) | |
| >=65 | 1670 | 99 | 5.9 | 1739 | 111 | 6.4 | 0.5808 | 1.08 | ( 0.83, 1.40) | 1.08 | ( 0.82, 1.43) | 0.00 | (-0.01, 0.02) | |
| Region | | | | | | | | | | | | | | 0.3828 |
| North America | 273 | 24 | 8.8 | 273 | 16 | 5.9 | 0.1889 | 0.67 | ( 0.36, 1.23) | 0.65 | ( 0.34, 1.24) | -0.03 | (-0.07, 0.01) | |
| Latin America | 511 | 17 | 3.3 | 504 | 17 | 3.4 | 0.9674 | 1.01 | ( 0.52, 1.96) | 1.01 | ( 0.51, 2.01) | 0.00 | (-0.02, 0.02) | |
| Europe | 865 | 44 | 5.1 | 894 | 48 | 5.4 | 0.7903 | 1.06 | ( 0.71, 1.57) | 1.06 | ( 0.70, 1.61) | 0.00 | (-0.02, 0.02) | |
| Asia | 231 | 19 | 8.2 | 248 | 31 | 12.5 | 0.1263 | 1.52 | ( 0.88, 2.61) | 1.59 | ( 0.87, 2.91) | 0.04 | (-0.01, 0.10) | |
| Other | 121 | 6 | 5.0 | 133 | 9 | 6.8 | 0.5415 | 1.36 | ( 0.50, 3.72) | 1.39 | ( 0.48, 4.03) | 0.02 | (-0.04, 0.08) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.1295 |
| Diabetic | 1045 | 47 | 4.5 | 1081 | 64 | 5.9 | 0.1404 | 1.32 | ( 0.91, 1.90) | 1.34 | ( 0.91, 1.97) | 0.01 | ( 0.00, 0.03) | |
| Non-Diabetic | 956 | 63 | 6.6 | 971 | 57 | 5.9 | 0.5133 | 0.89 | ( 0.63, 1.26) | 0.88 | ( 0.61, 1.28) | -0.01 | (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7353 |
| <30 | 1086 | 67 | 6.2 | 1094 | 70 | 6.4 | 0.8256 | 1.04 | ( 0.75, 1.43) | 1.04 | ( 0.74, 1.47) | 0.00 | (-0.02, 0.02) | |
| >=30 | 915 | 43 | 4.7 | 958 | 51 | 5.3 | 0.5363 | 1.13 | ( 0.76, 1.68) | 1.14 | ( 0.75, 1.73) | 0.01 | (-0.01, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7617 |
| <130 | 827 | 44 | 5.3 | 853 | 51 | 6.0 | 0.5591 | 1.12 | ( 0.76, 1.66) | 1.13 | ( 0.75, 1.71) | 0.01 | (-0.02, 0.03) | |
| >=130 | 1174 | 66 | 5.6 | 1199 | 70 | 5.8 | 0.8206 | 1.04 | ( 0.75, 1.44) | 1.04 | ( 0.74, 1.47) | 0.00 | (-0.02, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4766 |
| <75 | 935 | 56 | 6.0 | 934 | 63 | 6.7 | 0.5034 | 1.13 | ( 0.79, 1.60) | 1.14 | ( 0.78, 1.65) | 0.01 | (-0.01, 0.03) | |
| 75 to <85 | 657 | 31 | 4.7 | 703 | 40 | 5.7 | 0.4209 | 1.21 | ( 0.76, 1.90) | 1.22 | ( 0.75, 1.97) | 0.01 | (-0.01, 0.03) | |
| >=85 | 409 | 23 | 5.6 | 415 | 18 | 4.3 | 0.3959 | 0.77 | ( 0.42, 1.41) | 0.76 | ( 0.40, 1.43) | -0.01 | (-0.04, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.5693 |
| <30 | 161 | 7 | 4.3 | 148 | 11 | 7.4 | 0.2475 | 1.71 ( 0.68, 4.29) | 1.77 ( 0.67, 4.68) | 0.03 (-0.02, 0.08) | |
| 30 to <45 | 550 | 38 | 6.9 | 564 | 42 | 7.4 | 0.7282 | 1.08 ( 0.71, 1.65) | 1.08 ( 0.69, 1.71) | 0.01 (-0.02, 0.04) | |
| >=45 | 1289 | 65 | 5.0 | 1340 | 68 | 5.1 | 0.9702 | 1.01 ( 0.72, 1.40) | 1.01 ( 0.71, 1.43) | 0.00 (-0.02, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.2321 |
| Normal (<30) | 764 | 46 | 6.0 | 787 | 39 | 5.0 | 0.3567 | 0.82 ( 0.54, 1.25) | 0.81 ( 0.52, 1.26) | -0.01 (-0.03, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 48 | 5.2 | 938 | 65 | 6.9 | 0.1212 | 1.33 ( 0.93, 1.91) | 1.35 ( 0.92, 1.99) | 0.02 ( 0.00, 0.04) | |
| Macroalbuminuria (>300) | 311 | 15 | 4.8 | 318 | 17 | 5.3 | 0.7655 | 1.11 ( 0.56, 2.18) | 1.11 ( 0.55, 2.27) | 0.01 (-0.03, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.6042 |
| Low, moderate or high | 1477 | 75 | 5.1 | 1548 | 82 | 5.3 | 0.7858 | 1.04 ( 0.77, 1.42) | 1.05 ( 0.76, 1.44) | 0.00 (-0.01, 0.02) | |
| Very high | 519 | 34 | 6.6 | 495 | 39 | 7.9 | 0.4136 | 1.20 ( 0.77, 1.87) | 1.22 ( 0.76, 1.97) | 0.01 (-0.02, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.6804 |
| No | 411 | 30 | 7.3 | 410 | 35 | 8.5 | 0.5115 | 1.17 ( 0.73, 1.87) | 1.19 ( 0.71, 1.97) | 0.01 (-0.02, 0.05) | |
| Yes | 1590 | 80 | 5.0 | 1642 | 86 | 5.2 | 0.7908 | 1.04 ( 0.77, 1.40) | 1.04 ( 0.76, 1.43) | 0.00 (-0.01, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.3308 |
| No | 282 | 16 | 5.7 | 277 | 12 | 4.3 | 0.4672 | 0.76 ( 0.37, 1.58) | 0.75 ( 0.35, 1.62) | -0.01 (-0.05, 0.02) | |
| Yes | 1719 | 94 | 5.5 | 1775 | 109 | 6.1 | 0.3956 | 1.12 ( 0.86, 1.47) | 1.13 ( 0.85, 1.50) | 0.01 (-0.01, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9663 |
| No | 229 | 13 | 5.7 | 250 | 15 | 6.0 | 0.8803 | 1.06 ( 0.51, 2.17) | 1.06 ( 0.49, 2.28) | 0.00 (-0.04, 0.05) | |
| Yes | 1772 | 97 | 5.5 | 1802 | 106 | 5.9 | 0.5980 | 1.07 ( 0.82, 1.40) | 1.08 ( 0.81, 1.43) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 13 | 0.6 | 2052 | 16 | 0.8 | 0.6233 | 1.20 ( 0.58, | 2.49) | 1.20 ( 0.58, | 2.50) | 0.00 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | 0.7024 |
| Male | 1065 | 9 | 0.8 | 1093 | 10 | 0.9 | 0.8621 | 1.08 ( 0.44, | 2.65) | 1.08 ( 0.44, | 2.68) | 0.00 (-0.01, 0.01) | |
| Female | 936 | 4 | 0.4 | 959 | 6 | 0.6 | 0.5514 | 1.46 ( 0.41, | 5.17) | 1.47 ( 0.41, | 5.22) | 0.00 ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | 0.2367 |
| <65 | 331 | 2 | 0.6 | 313 | 0 | 0 | 0.2672 | 0.21 ( 0.01, | 4.39) | 0.21 ( 0.01, | 4.40) | -0.01 (-0.02, 0.00) | |
| >=65 | 1670 | 11 | 0.7 | 1739 | 16 | 0.9 | 0.3894 | 1.40 ( 0.65, | 3.00) | 1.40 ( 0.65, | 3.03) | 0.00 ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | 0.9293 |
| North America | 273 | 2 | 0.7 | 273 | 1 | 0.4 | 0.5626 | 0.50 ( 0.05, | 5.48) | 0.50 ( 0.04, | 5.53) | 0.00 (-0.02, 0.01) | |
| Latin America | 511 | 1 | 0.2 | 504 | 2 | 0.4 | 0.5551 | 2.03 ( 0.18, | 22.29) | 2.03 ( 0.18, | 22.48) | 0.00 ( 0.00, 0.01) | |
| Europe | 865 | 7 | 0.8 | 894 | 8 | 0.9 | 0.8452 | 1.11 ( 0.40, | 3.04) | 1.11 ( 0.40, | 3.07) | 0.00 (-0.01, 0.01) | |
| Asia | 231 | 2 | 0.9 | 248 | 3 | 1.2 | 0.7114 | 1.40 ( 0.24, | 8.29) | 1.40 ( 0.23, | 8.47) | 0.00 (-0.01, 0.02) | |
| Other | 121 | 1 | 0.8 | 133 | 2 | 1.5 | 0.6178 | 1.82 ( 0.17, | 19.81) | 1.83 ( 0.16, | 20.46) | 0.01 (-0.02, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.5182 |
| Diabetic | 1045 | 8 | 0.8 | 1081 | 8 | 0.7 | 0.9458 | 0.97 ( 0.36, | 2.57) | 0.97 ( 0.36, | 2.58) | 0.00 (-0.01, 0.01) | |
| Non-Diabetic | 956 | 5 | 0.5 | 971 | 8 | 0.8 | 0.4198 | 1.58 ( 0.52, | 4.80) | 1.58 ( 0.52, | 4.85) | 0.00 ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.5528 |
| <30 | 1086 | 6 | 0.6 | 1094 | 9 | 0.8 | 0.4455 | 1.49 ( 0.53, | 4.17) | 1.49 ( 0.53, | 4.21) | 0.00 ( 0.00, 0.01) | |
| >=30 | 915 | 7 | 0.8 | 958 | 7 | 0.7 | 0.9313 | 0.96 ( 0.34, | 2.71) | 0.95 ( 0.33, | 2.73) | 0.00 (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.4819 |
| <130 | 827 | 4 | 0.5 | 853 | 7 | 0.8 | 0.3919 | 1.70 ( 0.50, | 5.77) | 1.70 ( 0.50, | 5.84) | 0.00 ( 0.00, 0.01) | |
| >=130 | 1174 | 9 | 0.8 | 1199 | 9 | 0.8 | 0.9642 | 0.98 ( 0.39, | 2.46) | 0.98 ( 0.39, | 2.47) | 0.00 (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.6565 |
| <75 | 935 | 7 | 0.7 | 934 | 8 | 0.9 | 0.7938 | 1.14 ( 0.42, | 3.14) | 1.15 ( 0.41, | 3.17) | 0.00 (-0.01, 0.01) | |
| 75 to <85 | 657 | 3 | 0.5 | 703 | 6 | 0.9 | 0.3670 | 1.87 ( 0.47, | 7.44) | 1.88 ( 0.47, | 7.53) | 0.00 ( 0.00, 0.01) | |
| >=85 | 409 | 3 | 0.7 | 415 | 2 | 0.5 | 0.6420 | 0.66 ( 0.11, | 3.91) | 0.66 ( 0.11, | 3.94) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6431 |
| <30 | 161 | 1 | 0.6 | 148 | 3 | 2.0 | 0.2747 | 3.26 ( 0.34, 31.03) | 3.31 ( 0.34, 32.18) | 0.01 | (-0.01, 0.04) | |
| 30 to <45 | 550 | 2 | 0.4 | 564 | 2 | 0.4 | 0.9799 | 0.98 ( 0.14, 6.90) | 0.98 ( 0.14, 6.95) | 0.00 | (-0.01, 0.01) | |
| >=45 | 1289 | 10 | 0.8 | 1340 | 11 | 0.8 | 0.8967 | 1.06 ( 0.45, 2.48) | 1.06 ( 0.45, 2.50) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2010 |
| Normal (<30) | 764 | 10 | 1.3 | 787 | 7 | 0.9 | 0.4277 | 0.68 ( 0.26, 1.78) | 0.68 ( 0.26, 1.79) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 2 | 0.2 | 938 | 7 | 0.7 | 0.1003 | 3.44 ( 0.72, 16.50) | 3.45 ( 0.72, 16.67) | 0.01 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 311 | 1 | 0.3 | 318 | 2 | 0.6 | 0.5759 | 1.96 ( 0.18, 21.46) | 1.96 ( 0.18, 21.75) | 0.00 | (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2127 |
| Low, moderate or high | 1477 | 12 | 0.8 | 1548 | 12 | 0.8 | 0.9081 | 0.95 ( 0.43, 2.12) | 0.95 ( 0.43, 2.13) | 0.00 | (-0.01, 0.01) | |
| Very high | 519 | 1 | 0.2 | 495 | 4 | 0.8 | 0.1620 | 4.19 ( 0.47, 37.39) | 4.22 ( 0.47, 37.89) | 0.01 | ( 0.00, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.2315 |
| No | 411 | 1 | 0.2 | 410 | 4 | 1.0 | 0.1775 | 4.01 ( 0.45, 35.72) | 4.04 ( 0.45, 36.30) | 0.01 | ( 0.00, 0.02) | |
| Yes | 1590 | 12 | 0.8 | 1642 | 12 | 0.7 | 0.9369 | 0.97 ( 0.44, 2.15) | 0.97 ( 0.43, 2.16) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.1298 |
| No | 282 | 3 | 1.1 | 277 | 0 | 0 | 0.1369 | 0.15 (<0.01, 2.80) | 0.14 (<0.01, 2.80) | -0.01 | (-0.02, 0.00) | |
| Yes | 1719 | 10 | 0.6 | 1775 | 16 | 0.9 | 0.2717 | 1.55 ( 0.71, 3.40) | 1.55 ( 0.70, 3.44) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.4027 |
| No | 229 | 2 | 0.9 | 250 | 1 | 0.4 | 0.5118 | 0.46 ( 0.04, 5.02) | 0.46 ( 0.04, 5.06) | 0.00 | (-0.02, 0.01) | |
| Yes | 1772 | 11 | 0.6 | 1802 | 15 | 0.8 | 0.4566 | 1.34 ( 0.62, 2.91) | 1.34 ( 0.62, 2.93) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 229 | 11.4 | 2052 | 294 | 14.3 | 0.0062 | 1.25 ( 1.07, 1.47) | 1.29 ( 1.08, 1.56) | 0.03 ( 0.01, 0.05) | |
| Sex | | | | | | | | | | | 0.7834 |
| Male | 1065 | 124 | 11.6 | 1093 | 156 | 14.3 | 0.0692 | 1.23 ( 0.98, 1.53) | 1.26 ( 0.98, 1.63) | 0.03 ( 0.00, 0.05) | |
| Female | 936 | 105 | 11.2 | 959 | 138 | 14.4 | 0.0389 | 1.28 ( 1.01, 1.63) | 1.33 ( 1.01, 1.75) | 0.03 ( 0.00, 0.06) | |
| Age [years] | | | | | | | | | | | 0.3502 |
| <65 | 331 | 23 | 6.9 | 313 | 34 | 10.9 | 0.0805 | 1.56 ( 0.94, 2.59) | 1.63 ( 0.94, 2.84) | 0.04 ( 0.00, 0.08) | |
| >=65 | 1670 | 206 | 12.3 | 1739 | 260 | 15.0 | 0.0263 | 1.21 ( 1.02, 1.44) | 1.25 ( 1.03, 1.52) | 0.03 ( 0.00, 0.05) | |
| Region | | | | | | | | | | | 0.1438 |
| North America | 273 | 48 | 17.6 | 273 | 59 | 21.6 | 0.2356 | 1.23 ( 0.87, 1.73) | 1.29 ( 0.85, 1.98) | 0.04 (-0.03, 0.11) | |
| Latin America | 511 | 38 | 7.4 | 504 | 59 | 11.7 | 0.0207 | 1.57 ( 1.07, 2.32) | 1.65 ( 1.08, 2.53) | 0.04 ( 0.01, 0.08) | |
| Europe | 865 | 103 | 11.9 | 894 | 108 | 12.1 | 0.9111 | 1.01 ( 0.79, 1.31) | 1.02 ( 0.76, 1.36) | 0.00 (-0.03, 0.03) | |
| Asia | 231 | 27 | 11.7 | 248 | 38 | 15.3 | 0.2458 | 1.31 ( 0.83, 2.08) | 1.37 ( 0.81, 2.32) | 0.04 (-0.02, 0.10) | |
| Other | 121 | 13 | 10.7 | 133 | 30 | 22.6 | 0.0122 | 2.10 ( 1.15, 3.83) | 2.42 ( 1.20, 4.89) | 0.12 ( 0.03, 0.21) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.6803 |
| Diabetic | 1045 | 115 | 11.0 | 1081 | 144 | 13.3 | 0.1026 | 1.21 ( 0.96, 1.52) | 1.24 ( 0.96, 1.61) | 0.02 ( 0.00, 0.05) | |
| Non-Diabetic | 956 | 114 | 11.9 | 971 | 150 | 15.4 | 0.0245 | 1.30 ( 1.03, 1.62) | 1.35 ( 1.04, 1.75) | 0.04 ( 0.00, 0.07) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.8373 |
| <30 | 1086 | 121 | 11.1 | 1094 | 155 | 14.2 | 0.0336 | 1.27 ( 1.02, 1.59) | 1.32 ( 1.02, 1.70) | 0.03 ( 0.00, 0.06) | |
| >=30 | 915 | 108 | 11.8 | 958 | 139 | 14.5 | 0.0836 | 1.23 ( 0.97, 1.55) | 1.27 ( 0.97, 1.66) | 0.03 ( 0.00, 0.06) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.8740 |
| <130 | 827 | 114 | 13.8 | 853 | 149 | 17.5 | 0.0378 | 1.27 ( 1.01, 1.59) | 1.32 ( 1.02, 1.73) | 0.04 ( 0.00, 0.07) | |
| >=130 | 1174 | 115 | 9.8 | 1199 | 145 | 12.1 | 0.0732 | 1.23 ( 0.98, 1.56) | 1.27 ( 0.98, 1.64) | 0.02 ( 0.00, 0.05) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.5845 |
| <75 | 935 | 123 | 13.2 | 934 | 157 | 16.8 | 0.0269 | 1.28 ( 1.03, 1.59) | 1.33 ( 1.03, 1.72) | 0.04 ( 0.00, 0.07) | |
| 75 to <85 | 657 | 70 | 10.7 | 703 | 84 | 11.9 | 0.4516 | 1.12 ( 0.83, 1.51) | 1.14 ( 0.81, 1.59) | 0.01 (-0.02, 0.05) | |
| >=85 | 409 | 36 | 8.8 | 415 | 53 | 12.8 | 0.0665 | 1.45 ( 0.97, 2.17) | 1.52 ( 0.97, 2.37) | 0.04 ( 0.00, 0.08) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.0376 |
| <30 | 161 | 20 | 12.4 | 148 | 30 | 20.3 | 0.0613 | 1.63 | ( 0.97, 2.74) | 1.79 | ( 0.97, 3.32) | 0.08 ( 0.00, 0.16) | |
| 30 to <45 | 550 | 89 | 16.2 | 564 | 86 | 15.2 | 0.6686 | 0.94 | ( 0.72, 1.24) | 0.93 | ( 0.67, 1.29) | -0.01 (-0.05, 0.03) | |
| >=45 | 1289 | 120 | 9.3 | 1340 | 178 | 13.3 | 0.0013 | 1.43 | ( 1.15, 1.78) | 1.49 | ( 1.17, 1.91) | 0.04 ( 0.02, 0.06) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.3448 |
| Normal (<30) | 764 | 104 | 13.6 | 787 | 130 | 16.5 | 0.1099 | 1.21 | ( 0.96, 1.54) | 1.26 | ( 0.95, 1.66) | 0.03 (-0.01, 0.06) | |
| Microalbuminuria (30 to <=300) | 921 | 94 | 10.2 | 938 | 134 | 14.3 | 0.0073 | 1.40 | ( 1.09, 1.79) | 1.47 | ( 1.11, 1.94) | 0.04 ( 0.01, 0.07) | |
| Macroalbuminuria (>300) | 311 | 30 | 9.6 | 318 | 29 | 9.1 | 0.8208 | 0.95 | ( 0.58, 1.54) | 0.94 | ( 0.55, 1.61) | -0.01 (-0.05, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.7601 |
| Low, moderate or high | 1477 | 164 | 11.1 | 1548 | 213 | 13.8 | 0.0270 | 1.24 | ( 1.02, 1.50) | 1.28 | ( 1.03, 1.59) | 0.03 ( 0.00, 0.05) | |
| Very high | 519 | 64 | 12.3 | 495 | 80 | 16.2 | 0.0807 | 1.31 | ( 0.97, 1.78) | 1.37 | ( 0.96, 1.95) | 0.04 ( 0.00, 0.08) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.2626 |
| No | 411 | 51 | 12.4 | 410 | 53 | 12.9 | 0.8234 | 1.04 | ( 0.73, 1.49) | 1.05 | ( 0.69, 1.58) | 0.01 (-0.04, 0.05) | |
| Yes | 1590 | 178 | 11.2 | 1642 | 241 | 14.7 | 0.0032 | 1.31 | ( 1.09, 1.57) | 1.36 | ( 1.11, 1.68) | 0.03 ( 0.01, 0.06) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.8884 |
| No | 282 | 30 | 10.6 | 277 | 38 | 13.7 | 0.2653 | 1.29 | ( 0.82, 2.02) | 1.34 | ( 0.80, 2.22) | 0.03 (-0.02, 0.08) | |
| Yes | 1719 | 199 | 11.6 | 1775 | 256 | 14.4 | 0.0125 | 1.25 | ( 1.05, 1.48) | 1.29 | ( 1.06, 1.57) | 0.03 ( 0.01, 0.05) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.9478 |
| No | 229 | 15 | 6.6 | 250 | 21 | 8.4 | 0.4431 | 1.28 | ( 0.68, 2.43) | 1.31 | ( 0.66, 2.60) | 0.02 (-0.03, 0.07) | |
| Yes | 1772 | 214 | 12.1 | 1802 | 273 | 15.1 | 0.0074 | 1.25 | ( 1.06, 1.48) | 1.30 | ( 1.07, 1.58) | 0.03 ( 0.01, 0.05) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 204 | 10.2 | 2052 | 251 | 12.2 | 0.0400 | 1.20 ( 1.01, 1.43) | 1.23 ( 1.01, 1.49) | 0.02 ( 0.00, 0.04) | |
| Sex | | | | | | | | | | | 0.8097 |
| Male | 1065 | 111 | 10.4 | 1093 | 134 | 12.3 | 0.1786 | 1.18 ( 0.93, 1.49) | 1.20 ( 0.92, 1.57) | 0.02 (-0.01, 0.05) | |
| Female | 936 | 93 | 9.9 | 959 | 117 | 12.2 | 0.1164 | 1.23 ( 0.95, 1.59) | 1.26 ( 0.94, 1.68) | 0.02 (-0.01, 0.05) | |
| Age [years] | | | | | | | | | | | 0.2364 |
| <65 | 331 | 21 | 6.3 | 313 | 32 | 10.2 | 0.0734 | 1.61 ( 0.95, 2.73) | 1.68 ( 0.95, 2.98) | 0.04 ( 0.00, 0.08) | |
| >=65 | 1670 | 183 | 11.0 | 1739 | 219 | 12.6 | 0.1389 | 1.15 ( 0.96, 1.38) | 1.17 ( 0.95, 1.44) | 0.02 (-0.01, 0.04) | |
| Region | | | | | | | | | | | 0.0944 |
| North America | 273 | 46 | 16.8 | 273 | 55 | 20.1 | 0.3212 | 1.20 ( 0.84, 1.70) | 1.25 ( 0.81, 1.92) | 0.03 (-0.03, 0.10) | |
| Latin America | 511 | 33 | 6.5 | 504 | 55 | 10.9 | 0.0117 | 1.69 ( 1.12, 2.56) | 1.77 ( 1.13, 2.78) | 0.04 ( 0.01, 0.08) | |
| Europe | 865 | 95 | 11.0 | 894 | 93 | 10.4 | 0.6939 | 0.95 ( 0.72, 1.24) | 0.94 ( 0.70, 1.27) | -0.01 (-0.03, 0.02) | |
| Asia | 231 | 18 | 7.8 | 248 | 22 | 8.9 | 0.6698 | 1.14 ( 0.63, 2.07) | 1.15 ( 0.60, 2.21) | 0.01 (-0.04, 0.06) | |
| Other | 121 | 12 | 9.9 | 133 | 26 | 19.5 | 0.0316 | 1.97 ( 1.04, 3.73) | 2.21 ( 1.06, 4.60) | 0.10 ( 0.01, 0.18) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.7226 |
| Diabetic | 1045 | 99 | 9.5 | 1081 | 119 | 11.0 | 0.2436 | 1.16 ( 0.90, 1.50) | 1.18 ( 0.89, 1.57) | 0.02 (-0.01, 0.04) | |
| Non-Diabetic | 956 | 105 | 11.0 | 971 | 132 | 13.6 | 0.0810 | 1.24 ( 0.97, 1.57) | 1.28 ( 0.97, 1.68) | 0.03 ( 0.00, 0.06) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.8254 |
| <30 | 1086 | 104 | 9.6 | 1094 | 128 | 11.7 | 0.1079 | 1.22 ( 0.96, 1.56) | 1.25 ( 0.95, 1.64) | 0.02 ( 0.00, 0.05) | |
| >=30 | 915 | 100 | 10.9 | 958 | 123 | 12.8 | 0.2019 | 1.17 ( 0.92, 1.51) | 1.20 ( 0.91, 1.59) | 0.02 (-0.01, 0.05) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.8822 |
| <130 | 827 | 103 | 12.5 | 853 | 129 | 15.1 | 0.1130 | 1.21 ( 0.95, 1.54) | 1.25 ( 0.95, 1.66) | 0.03 (-0.01, 0.06) | |
| >=130 | 1174 | 101 | 8.6 | 1199 | 122 | 10.2 | 0.1895 | 1.18 ( 0.92, 1.52) | 1.20 ( 0.91, 1.59) | 0.02 (-0.01, 0.04) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.1108 |
| <75 | 935 | 108 | 11.6 | 934 | 133 | 14.2 | 0.0829 | 1.23 ( 0.97, 1.56) | 1.27 ( 0.97, 1.67) | 0.03 ( 0.00, 0.06) | |
| 75 to <85 | 657 | 66 | 10.0 | 703 | 67 | 9.5 | 0.7493 | 0.95 ( 0.69, 1.31) | 0.94 ( 0.66, 1.35) | -0.01 (-0.04, 0.03) | |
| >=85 | 409 | 30 | 7.3 | 415 | 51 | 12.3 | 0.0169 | 1.68 ( 1.09, 2.58) | 1.77 ( 1.10, 2.84) | 0.05 ( 0.01, 0.09) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0618 |
| <30 | 161 | 17 | 10.6 | 148 | 25 | 16.9 | 0.1046 | 1.60 ( 0.90, 2.84) | 1.72 ( 0.89, 3.34) | 0.06 (-0.01, 0.14) | |
| 30 to <45 | 550 | 77 | 14.0 | 564 | 71 | 12.6 | 0.4878 | 0.90 ( 0.67, 1.21) | 0.88 ( 0.63, 1.25) | -0.01 (-0.05, 0.03) | |
| >=45 | 1289 | 110 | 8.5 | 1340 | 155 | 11.6 | 0.0098 | 1.36 ( 1.07, 1.71) | 1.40 ( 1.08, 1.81) | 0.03 ( 0.01, 0.05) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.4580 |
| Normal (<30) | 764 | 93 | 12.2 | 787 | 113 | 14.4 | 0.2048 | 1.18 ( 0.91, 1.52) | 1.21 ( 0.90, 1.62) | 0.02 (-0.01, 0.06) | |
| Microalbuminuria (30 to <=300) | 921 | 85 | 9.2 | 938 | 114 | 12.2 | 0.0414 | 1.32 ( 1.01, 1.72) | 1.36 ( 1.01, 1.83) | 0.03 ( 0.00, 0.06) | |
| Macroalbuminuria (>300) | 311 | 25 | 8.0 | 318 | 23 | 7.2 | 0.7035 | 0.90 ( 0.52, 1.55) | 0.89 ( 0.49, 1.61) | -0.01 (-0.05, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.6176 |
| Low, moderate or high | 1477 | 148 | 10.0 | 1548 | 182 | 11.8 | 0.1256 | 1.17 ( 0.96, 1.44) | 1.20 ( 0.95, 1.51) | 0.02 ( 0.00, 0.04) | |
| Very high | 519 | 55 | 10.6 | 495 | 68 | 13.7 | 0.1258 | 1.30 ( 0.93, 1.81) | 1.34 ( 0.92, 1.96) | 0.03 (-0.01, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3056 |
| No | 411 | 46 | 11.2 | 410 | 46 | 11.2 | 0.9901 | 1.00 ( 0.68, 1.47) | 1.00 ( 0.65, 1.55) | 0.00 (-0.04, 0.04) | |
| Yes | 1590 | 158 | 9.9 | 1642 | 205 | 12.5 | 0.0218 | 1.26 ( 1.03, 1.53) | 1.29 ( 1.04, 1.61) | 0.03 ( 0.00, 0.05) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6047 |
| No | 282 | 24 | 8.5 | 277 | 32 | 11.6 | 0.2311 | 1.36 ( 0.82, 2.24) | 1.40 ( 0.80, 2.45) | 0.03 (-0.02, 0.08) | |
| Yes | 1719 | 180 | 10.5 | 1775 | 219 | 12.3 | 0.0828 | 1.18 ( 0.98, 1.42) | 1.20 ( 0.98, 1.48) | 0.02 ( 0.00, 0.04) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9694 |
| No | 229 | 12 | 5.2 | 250 | 16 | 6.4 | 0.5889 | 1.22 ( 0.59, 2.53) | 1.24 ( 0.57, 2.67) | 0.01 (-0.03, 0.05) | |
| Yes | 1772 | 192 | 10.8 | 1802 | 235 | 13.0 | 0.0421 | 1.20 ( 1.01, 1.44) | 1.23 ( 1.01, 1.51) | 0.02 ( 0.00, 0.04) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 2001 | 365 | 18.2 | 2052 | 353 | 17.2 | 0.3868 | 0.94 ( 0.83, | 1.08) | 0.93 ( 0.79, | 1.09) | -0.01 (-0.03, | 0.01) | |
| Sex | | | | | | | | | | | | | | 0.4953 |
| Male | 1065 | 191 | 17.9 | 1093 | 193 | 17.7 | 0.8667 | 0.98 ( 0.82, | 1.18) | 0.98 ( 0.79, | 1.22) | 0.00 (-0.04, | 0.03) | |
| Female | 936 | 174 | 18.6 | 959 | 160 | 16.7 | 0.2764 | 0.90 ( 0.74, | 1.09) | 0.88 ( 0.69, | 1.11) | -0.02 (-0.05, | 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.6627 |
| <65 | 331 | 63 | 19.0 | 313 | 60 | 19.2 | 0.9650 | 1.01 ( 0.73, | 1.38) | 1.01 ( 0.68, | 1.49) | 0.00 (-0.06, | 0.06) | |
| >=65 | 1670 | 302 | 18.1 | 1739 | 293 | 16.8 | 0.3423 | 0.93 ( 0.81, | 1.08) | 0.92 ( 0.77, | 1.10) | -0.01 (-0.04, | 0.01) | |
| Region | | | | | | | | | | | | | | 0.7842 |
| North America | 273 | 72 | 26.4 | 273 | 60 | 22.0 | 0.2303 | 0.83 ( 0.62, | 1.12) | 0.79 ( 0.53, | 1.17) | -0.04 (-0.12, | 0.03) | |
| Latin America | 511 | 90 | 17.6 | 504 | 92 | 18.3 | 0.7900 | 1.04 ( 0.80, | 1.35) | 1.04 ( 0.76, | 1.44) | 0.01 (-0.04, | 0.05) | |
| Europe | 865 | 143 | 16.5 | 894 | 133 | 14.9 | 0.3401 | 0.90 ( 0.72, | 1.12) | 0.88 ( 0.68, | 1.14) | -0.02 (-0.05, | 0.02) | |
| Asia | 231 | 31 | 13.4 | 248 | 35 | 14.1 | 0.8260 | 1.05 ( 0.67, | 1.65) | 1.06 ( 0.63, | 1.78) | 0.01 (-0.05, | 0.07) | |
| Other | 121 | 29 | 24.0 | 133 | 33 | 24.8 | 0.8756 | 1.04 ( 0.67, | 1.60) | 1.05 ( 0.59, | 1.86) | 0.01 (-0.10, | 0.11) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0682 |
| Diabetic | 1045 | 211 | 20.2 | 1081 | 227 | 21.0 | 0.6453 | 1.04 ( 0.88, | 1.23) | 1.05 ( 0.85, | 1.30) | 0.01 (-0.03, | 0.04) | |
| Non-Diabetic | 956 | 154 | 16.1 | 971 | 126 | 13.0 | 0.0511 | 0.81 ( 0.65, | >1.00) | 0.78 ( 0.60, | 1.00) | -0.03 (-0.06, | 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3014 |
| <30 | 1086 | 190 | 17.5 | 1094 | 168 | 15.4 | 0.1777 | 0.88 ( 0.73, | 1.06) | 0.86 ( 0.68, | 1.07) | -0.02 (-0.05, | 0.01) | |
| >=30 | 915 | 175 | 19.1 | 958 | 185 | 19.3 | 0.9189 | 1.01 ( 0.84, | 1.22) | 1.01 ( 0.80, | 1.27) | 0.00 (-0.03, | 0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6766 |
| <130 | 827 | 144 | 17.4 | 853 | 145 | 17.0 | 0.8224 | 0.98 ( 0.79, | 1.20) | 0.97 ( 0.75, | 1.25) | 0.00 (-0.04, | 0.03) | |
| >=130 | 1174 | 221 | 18.8 | 1199 | 208 | 17.3 | 0.3500 | 0.92 ( 0.78, | 1.09) | 0.91 ( 0.73, | 1.12) | -0.01 (-0.05, | 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3650 |
| <75 | 935 | 175 | 18.7 | 934 | 181 | 19.4 | 0.7154 | 1.04 ( 0.86, | 1.25) | 1.04 ( 0.83, | 1.32) | 0.01 (-0.03, | 0.04) | |
| 75 to <85 | 657 | 125 | 19.0 | 703 | 112 | 15.9 | 0.1328 | 0.84 ( 0.66, | 1.06) | 0.81 ( 0.61, | 1.07) | -0.03 (-0.07, | 0.01) | |
| >=85 | 409 | 65 | 15.9 | 415 | 60 | 14.5 | 0.5660 | 0.91 ( 0.66, | 1.26) | 0.89 ( 0.61, | 1.31) | -0.01 (-0.06, | 0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.5927 |
| <30 | 161 | 60 | 37.3 | 148 | 45 | 30.4 | 0.2033 | 0.82 ( 0.60, 1.12) | 0.74 ( 0.46, 1.18) | -0.07 (-0.17, 0.04) | |
| 30 to <45 | 550 | 128 | 23.3 | 564 | 129 | 22.9 | 0.8740 | 0.98 ( 0.79, 1.22) | 0.98 ( 0.74, 1.29) | 0.00 (-0.05, 0.05) | |
| >=45 | 1289 | 177 | 13.7 | 1340 | 179 | 13.4 | 0.7797 | 0.97 ( 0.80, 1.18) | 0.97 ( 0.77, 1.21) | 0.00 (-0.03, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.5330 |
| Normal (<30) | 764 | 127 | 16.6 | 787 | 120 | 15.2 | 0.4593 | 0.92 ( 0.73, 1.15) | 0.90 ( 0.69, 1.18) | -0.01 (-0.05, 0.02) | |
| Microalbuminuria (30 to <=300) | 921 | 149 | 16.2 | 938 | 156 | 16.6 | 0.7920 | 1.03 ( 0.84, 1.26) | 1.03 ( 0.81, 1.32) | 0.00 (-0.03, 0.04) | |
| Macroalbuminuria (>300) | 311 | 88 | 28.3 | 318 | 77 | 24.2 | 0.2446 | 0.86 ( 0.66, 1.11) | 0.81 ( 0.57, 1.16) | -0.04 (-0.11, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.9305 |
| Low, moderate or high | 1477 | 213 | 14.4 | 1548 | 215 | 13.9 | 0.6746 | 0.96 ( 0.81, 1.15) | 0.96 ( 0.78, 1.17) | -0.01 (-0.03, 0.02) | |
| Very high | 519 | 152 | 29.3 | 495 | 138 | 27.9 | 0.6199 | 0.95 ( 0.78, 1.16) | 0.93 ( 0.71, 1.23) | -0.01 (-0.07, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.5599 |
| No | 411 | 76 | 18.5 | 410 | 66 | 16.1 | 0.3645 | 0.87 ( 0.64, 1.18) | 0.85 ( 0.59, 1.22) | -0.02 (-0.08, 0.03) | |
| Yes | 1590 | 289 | 18.2 | 1642 | 287 | 17.5 | 0.6045 | 0.96 ( 0.83, 1.12) | 0.95 ( 0.80, 1.14) | -0.01 (-0.03, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.8028 |
| No | 282 | 56 | 19.9 | 277 | 54 | 19.5 | 0.9139 | 0.98 ( 0.70, 1.37) | 0.98 ( 0.64, 1.48) | 0.00 (-0.07, 0.06) | |
| Yes | 1719 | 309 | 18.0 | 1775 | 299 | 16.8 | 0.3782 | 0.94 ( 0.81, 1.08) | 0.92 ( 0.78, 1.10) | -0.01 (-0.04, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.2498 |
| No | 229 | 33 | 14.4 | 250 | 26 | 10.4 | 0.1822 | 0.72 ( 0.45, 1.17) | 0.69 ( 0.40, 1.19) | -0.04 (-0.10, 0.02) | |
| Yes | 1772 | 332 | 18.7 | 1802 | 327 | 18.1 | 0.6496 | 0.97 ( 0.84, 1.11) | 0.96 ( 0.81, 1.14) | -0.01 (-0.03, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 84 | 4.2 | 2052 | 56 | 2.7 | 0.0105 | 0.65 ( 0.47, 0.91) | 0.64 ( 0.45, 0.90) | -0.01 (-0.03, 0.00) | |
| Sex | | | | | | | | | | | 0.0019 |
| Male | 1065 | 44 | 4.1 | 1093 | 44 | 4.0 | 0.9011 | 0.97 ( 0.65, 1.47) | 0.97 ( 0.64, 1.49) | 0.00 (-0.02, 0.02) | |
| Female | 936 | 40 | 4.3 | 959 | 12 | 1.3 | <0.0001 | 0.29 ( 0.15, 0.55) | 0.28 ( 0.15, 0.54) | -0.03 (-0.04,-0.02) | |
| Age [years] | | | | | | | | | | | 0.0380 |
| <65 | 331 | 12 | 3.6 | 313 | 15 | 4.8 | 0.4602 | 1.32 ( 0.63, 2.78) | 1.34 ( 0.62, 2.91) | 0.01 (-0.02, 0.04) | |
| >=65 | 1670 | 72 | 4.3 | 1739 | 41 | 2.4 | 0.0014 | 0.55 ( 0.37, 0.80) | 0.54 ( 0.36, 0.79) | -0.02 (-0.03,-0.01) | |
| Region | | | | | | | | | | | 0.4552 |
| North America | 273 | 25 | 9.2 | 273 | 15 | 5.5 | 0.1005 | 0.60 ( 0.32, 1.11) | 0.58 ( 0.30, 1.12) | -0.04 (-0.08, 0.01) | |
| Latin America | 511 | 12 | 2.3 | 504 | 6 | 1.2 | 0.1623 | 0.51 ( 0.19, 1.34) | 0.50 ( 0.19, 1.35) | -0.01 (-0.03, 0.00) | |
| Europe | 865 | 24 | 2.8 | 894 | 18 | 2.0 | 0.2959 | 0.73 ( 0.40, 1.33) | 0.72 ( 0.39, 1.34) | -0.01 (-0.02, 0.01) | |
| Asia | 231 | 6 | 2.6 | 248 | 9 | 3.6 | 0.5171 | 1.40 ( 0.51, 3.86) | 1.41 ( 0.49, 4.03) | 0.01 (-0.02, 0.04) | |
| Other | 121 | 17 | 14.0 | 133 | 8 | 6.0 | 0.0318 | 0.43 ( 0.19, 0.96) | 0.39 ( 0.16, 0.94) | -0.08 (-0.15,-0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.6619 |
| Diabetic | 1045 | 40 | 3.8 | 1081 | 29 | 2.7 | 0.1364 | 0.70 ( 0.44, 1.12) | 0.69 ( 0.43, 1.13) | -0.01 (-0.03, 0.00) | |
| Non-Diabetic | 956 | 44 | 4.6 | 971 | 27 | 2.8 | 0.0338 | 0.60 ( 0.38, 0.97) | 0.59 ( 0.36, 0.97) | -0.02 (-0.04, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.3469 |
| <30 | 1086 | 48 | 4.4 | 1094 | 27 | 2.5 | 0.0124 | 0.56 ( 0.35, 0.89) | 0.55 ( 0.34, 0.88) | -0.02 (-0.03, 0.00) | |
| >=30 | 915 | 36 | 3.9 | 958 | 29 | 3.0 | 0.2835 | 0.77 ( 0.48, 1.24) | 0.76 ( 0.46, 1.25) | -0.01 (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.9208 |
| <130 | 827 | 41 | 5.0 | 853 | 27 | 3.2 | 0.0624 | 0.64 ( 0.40, 1.03) | 0.63 ( 0.38, 1.03) | -0.02 (-0.04, 0.00) | |
| >=130 | 1174 | 43 | 3.7 | 1199 | 29 | 2.4 | 0.0773 | 0.66 ( 0.42, 1.05) | 0.65 ( 0.40, 1.05) | -0.01 (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.6886 |
| <75 | 935 | 43 | 4.6 | 934 | 32 | 3.4 | 0.1965 | 0.74 ( 0.48, 1.17) | 0.74 ( 0.46, 1.17) | -0.01 (-0.03, 0.01) | |
| 75 to <85 | 657 | 29 | 4.4 | 703 | 17 | 2.4 | 0.0419 | 0.55 ( 0.30, 0.99) | 0.54 ( 0.29, 0.99) | -0.02 (-0.04, 0.00) | |
| >=85 | 409 | 12 | 2.9 | 415 | 7 | 1.7 | 0.2330 | 0.57 ( 0.23, 1.45) | 0.57 ( 0.22, 1.46) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.7508 |
| <30 | 161 | 11 | 6.8 | 148 | 9 | 6.1 | 0.7886 | 0.89 ( 0.38, 2.09) | 0.88 ( 0.36, 2.19) | -0.01 (-0.06, 0.05) | |
| 30 to <45 | 550 | 31 | 5.6 | 564 | 20 | 3.5 | 0.0952 | 0.63 ( 0.36, 1.09) | 0.62 ( 0.35, 1.09) | -0.02 (-0.05, 0.00) | |
| >=45 | 1289 | 42 | 3.3 | 1340 | 27 | 2.0 | 0.0462 | 0.62 ( 0.38, <1.00) | 0.61 ( 0.37, 1.00) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.0387 |
| Normal (<30) | 764 | 41 | 5.4 | 787 | 18 | 2.3 | 0.0015 | 0.43 ( 0.25, 0.74) | 0.41 ( 0.23, 0.73) | -0.03 (-0.05,-0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 36 | 3.9 | 938 | 26 | 2.8 | 0.1722 | 0.71 ( 0.43, 1.16) | 0.70 ( 0.42, 1.17) | -0.01 (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 311 | 7 | 2.3 | 318 | 12 | 3.8 | 0.2646 | 1.68 ( 0.67, 4.20) | 1.70 ( 0.66, 4.38) | 0.02 (-0.01, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0993 |
| Low, moderate or high | 1477 | 56 | 3.8 | 1548 | 31 | 2.0 | 0.0033 | 0.53 ( 0.34, 0.81) | 0.52 ( 0.33, 0.81) | -0.02 (-0.03,-0.01) | |
| Very high | 519 | 28 | 5.4 | 495 | 25 | 5.1 | 0.8054 | 0.94 ( 0.55, 1.58) | 0.93 ( 0.54, 1.62) | 0.00 (-0.03, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.7154 |
| No | 411 | 27 | 6.6 | 410 | 16 | 3.9 | 0.0863 | 0.59 ( 0.33, 1.09) | 0.58 ( 0.31, 1.09) | -0.03 (-0.06, 0.00) | |
| Yes | 1590 | 57 | 3.6 | 1642 | 40 | 2.4 | 0.0557 | 0.68 ( 0.46, 1.01) | 0.67 ( 0.45, 1.01) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.9277 |
| No | 282 | 9 | 3.2 | 277 | 6 | 2.2 | 0.4532 | 0.68 ( 0.24, 1.88) | 0.67 ( 0.24, 1.91) | -0.01 (-0.04, 0.02) | |
| Yes | 1719 | 75 | 4.4 | 1775 | 50 | 2.8 | 0.0139 | 0.65 ( 0.45, 0.92) | 0.64 ( 0.44, 0.91) | -0.02 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9456 |
| No | 229 | 4 | 1.7 | 250 | 3 | 1.2 | 0.6184 | 0.69 ( 0.16, 3.04) | 0.68 ( 0.15, 3.09) | -0.01 (-0.03, 0.02) | |
| Yes | 1772 | 80 | 4.5 | 1802 | 53 | 2.9 | 0.0130 | 0.65 ( 0.46, 0.92) | 0.64 ( 0.45, 0.91) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 20 | 1.0 | 2052 | 25 | 1.2 | 0.5062 | 1.22 | ( 0.68, 2.19) | 1.22 | ( 0.68, 2.21) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.5371 |
| Male | 1065 | 13 | 1.2 | 1093 | 14 | 1.3 | 0.8999 | 1.05 | ( 0.50, 2.22) | 1.05 | ( 0.49, 2.24) | 0.00 | (-0.01, 0.01) | |
| Female | 936 | 7 | 0.7 | 959 | 11 | 1.1 | 0.3704 | 1.53 | ( 0.60, 3.94) | 1.54 | ( 0.59, 3.99) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.2975 |
| <65 | 331 | 4 | 1.2 | 313 | 2 | 0.6 | 0.4522 | 0.53 | ( 0.10, 2.87) | 0.53 | ( 0.10, 2.89) | -0.01 | (-0.02, 0.01) | |
| >=65 | 1670 | 16 | 1.0 | 1739 | 23 | 1.3 | 0.3171 | 1.38 | ( 0.73, 2.60) | 1.39 | ( 0.73, 2.63) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.8934 |
| North America | 273 | 4 | 1.5 | 273 | 6 | 2.2 | 0.5233 | 1.50 | ( 0.43, 5.26) | 1.51 | ( 0.42, 5.42) | 0.01 | (-0.02, 0.03) | |
| Latin America | 511 | 7 | 1.4 | 504 | 5 | 1.0 | 0.5777 | 0.72 | ( 0.23, 2.27) | 0.72 | ( 0.23, 2.29) | 0.00 | (-0.02, 0.01) | |
| Europe | 865 | 4 | 0.5 | 894 | 6 | 0.7 | 0.5605 | 1.45 | ( 0.41, 5.13) | 1.45 | ( 0.41, 5.17) | 0.00 | ( 0.00, 0.01) | |
| Asia | 231 | 3 | 1.3 | 248 | 5 | 2.0 | 0.5404 | 1.55 | ( 0.38, 6.42) | 1.56 | ( 0.37, 6.62) | 0.01 | (-0.02, 0.03) | |
| Other | 121 | 2 | 1.7 | 133 | 3 | 2.3 | 0.7298 | 1.36 | ( 0.23, 8.03) | 1.37 | ( 0.23, 8.36) | 0.01 | (-0.03, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6800 |
| Diabetic | 1045 | 19 | 1.8 | 1081 | 23 | 2.1 | 0.6082 | 1.17 | ( 0.64, 2.14) | 1.17 | ( 0.64, 2.17) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 956 | 1 | 0.1 | 971 | 2 | 0.2 | 0.5725 | 1.97 | ( 0.18, 21.68) | 1.97 | ( 0.18, 21.77) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1631 |
| <30 | 1086 | 8 | 0.7 | 1094 | 15 | 1.4 | 0.1471 | 1.86 | ( 0.79, 4.37) | 1.87 | ( 0.79, 4.44) | 0.01 | ( 0.00, 0.01) | |
| >=30 | 915 | 12 | 1.3 | 958 | 10 | 1.0 | 0.5910 | 0.80 | ( 0.35, 1.83) | 0.79 | ( 0.34, 1.85) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7699 |
| <130 | 827 | 8 | 1.0 | 853 | 9 | 1.1 | 0.8574 | 1.09 | ( 0.42, 2.81) | 1.09 | ( 0.42, 2.84) | 0.00 | (-0.01, 0.01) | |
| >=130 | 1174 | 12 | 1.0 | 1199 | 16 | 1.3 | 0.4812 | 1.31 | ( 0.62, 2.75) | 1.31 | ( 0.62, 2.78) | 0.00 | (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6243 |
| <75 | 935 | 10 | 1.1 | 934 | 11 | 1.2 | 0.8244 | 1.10 | ( 0.47, 2.58) | 1.10 | ( 0.47, 2.61) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 657 | 6 | 0.9 | 703 | 11 | 1.6 | 0.2799 | 1.71 | ( 0.64, 4.61) | 1.72 | ( 0.63, 4.69) | 0.01 | (-0.01, 0.02) | |
| >=85 | 409 | 4 | 1.0 | 415 | 3 | 0.7 | 0.6899 | 0.74 | ( 0.17, 3.28) | 0.74 | ( 0.16, 3.31) | 0.00 | (-0.02, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0658 |
| <30 | 161 | 3 | 1.9 | 148 | 7 | 4.7 | 0.1549 | 2.54 ( 0.67, 9.64) | 2.61 ( 0.66, 10.30) | 0.03 (-0.01, 0.07) | |
| 30 to <45 | 550 | 3 | 0.5 | 564 | 9 | 1.6 | 0.0895 | 2.93 ( 0.80, 10.75) | 2.96 ( 0.80, 10.98) | 0.01 ( 0.00, 0.02) | |
| >=45 | 1289 | 14 | 1.1 | 1340 | 9 | 0.7 | 0.2539 | 0.62 ( 0.27, 1.42) | 0.62 ( 0.27, 1.43) | 0.00 (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.8745 |
| Normal (<30) | 764 | 5 | 0.7 | 787 | 5 | 0.6 | 0.9625 | 0.97 ( 0.28, 3.34) | 0.97 ( 0.28, 3.37) | 0.00 (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 9 | 1.0 | 938 | 13 | 1.4 | 0.4152 | 1.42 ( 0.61, 3.30) | 1.42 ( 0.61, 3.35) | 0.00 (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 311 | 6 | 1.9 | 318 | 7 | 2.2 | 0.8105 | 1.14 ( 0.39, 3.36) | 1.14 ( 0.38, 3.44) | 0.00 (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.5745 |
| Low, moderate or high | 1477 | 10 | 0.7 | 1548 | 11 | 0.7 | 0.9116 | 1.05 ( 0.45, 2.46) | 1.05 ( 0.44, 2.48) | 0.00 (-0.01, 0.01) | |
| Very high | 519 | 10 | 1.9 | 495 | 14 | 2.8 | 0.3452 | 1.47 ( 0.66, 3.27) | 1.48 ( 0.65, 3.37) | 0.01 (-0.01, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3972 |
| No | 411 | 5 | 1.2 | 410 | 9 | 2.2 | 0.2789 | 1.80 ( 0.61, 5.34) | 1.82 ( 0.61, 5.49) | 0.01 (-0.01, 0.03) | |
| Yes | 1590 | 15 | 0.9 | 1642 | 16 | 1.0 | 0.9279 | 1.03 ( 0.51, 2.08) | 1.03 ( 0.51, 2.10) | 0.00 (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.7912 |
| No | 282 | 2 | 0.7 | 277 | 3 | 1.1 | 0.6388 | 1.53 ( 0.26, 9.07) | 1.53 ( 0.25, 9.24) | 0.00 (-0.01, 0.02) | |
| Yes | 1719 | 18 | 1.0 | 1775 | 22 | 1.2 | 0.5932 | 1.18 ( 0.64, 2.20) | 1.19 ( 0.63, 2.22) | 0.00 (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.6582 |
| No | 229 | 4 | 1.7 | 250 | 4 | 1.6 | 0.9004 | 0.92 ( 0.23, 3.62) | 0.91 ( 0.23, 3.70) | 0.00 (-0.02, 0.02) | |
| Yes | 1772 | 16 | 0.9 | 1802 | 21 | 1.2 | 0.4383 | 1.29 ( 0.68, 2.47) | 1.29 ( 0.67, 2.49) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 2001 | 195 | 9.7 | 2052 | 169 | 8.2 | 0.0929 | 0.85 ( 0.69, | 1.03) | 0.83 ( 0.67, | 1.03) | -0.02 (-0.03, | 0.00) | |
| Sex | | | | | | | | | | | | | | 0.1610 |
| Male | 1065 | 104 | 9.8 | 1093 | 102 | 9.3 | 0.7321 | 0.96 ( 0.74, | 1.24) | 0.95 ( 0.71, | 1.27) | 0.00 (-0.03, | 0.02) | |
| Female | 936 | 91 | 9.7 | 959 | 67 | 7.0 | 0.0313 | 0.72 ( 0.53, | 0.97) | 0.70 ( 0.50, | 0.97) | -0.03 (-0.05, | 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.5542 |
| <65 | 331 | 40 | 12.1 | 313 | 36 | 11.5 | 0.8187 | 0.95 ( 0.62, | 1.45) | 0.95 ( 0.59, | 1.53) | -0.01 (-0.06, | 0.04) | |
| >=65 | 1670 | 155 | 9.3 | 1739 | 133 | 7.6 | 0.0865 | 0.82 ( 0.66, | 1.03) | 0.81 ( 0.64, | 1.03) | -0.02 (-0.04, | 0.00) | |
| Region | | | | | | | | | | | | | | 0.0900 |
| North America | 273 | 20 | 7.3 | 273 | 32 | 11.7 | 0.0802 | 1.60 ( 0.94, | 2.73) | 1.68 ( 0.93, | 3.02) | 0.04 (-0.01, | 0.09) | |
| Latin America | 511 | 65 | 12.7 | 504 | 48 | 9.5 | 0.1055 | 0.75 ( 0.53, | 1.06) | 0.72 ( 0.49, | 1.07) | -0.03 (-0.07, | 0.01) | |
| Europe | 865 | 68 | 7.9 | 894 | 55 | 6.2 | 0.1600 | 0.78 ( 0.56, | 1.10) | 0.77 ( 0.53, | 1.11) | -0.02 (-0.04, | 0.01) | |
| Asia | 231 | 27 | 11.7 | 248 | 17 | 6.9 | 0.0672 | 0.59 ( 0.33, | 1.05) | 0.56 ( 0.29, | 1.05) | -0.05 (-0.10, | 0.00) | |
| Other | 121 | 15 | 12.4 | 133 | 17 | 12.8 | 0.9264 | 1.03 ( 0.54, | 1.97) | 1.04 ( 0.49, | 2.18) | 0.00 (-0.08, | 0.09) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3102 |
| Diabetic | 1045 | 131 | 12.5 | 1081 | 106 | 9.8 | 0.0455 | 0.78 ( 0.61, | <1.00) | 0.76 ( 0.58, | 1.00) | -0.03 (-0.05, | 0.00) | |
| Non-Diabetic | 956 | 64 | 6.7 | 971 | 63 | 6.5 | 0.8551 | 0.97 ( 0.69, | 1.36) | 0.97 ( 0.67, | 1.39) | 0.00 (-0.02, | 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4892 |
| <30 | 1086 | 109 | 10.0 | 1094 | 87 | 8.0 | 0.0889 | 0.79 ( 0.61, | 1.04) | 0.77 ( 0.58, | 1.04) | -0.02 (-0.04, | 0.00) | |
| >=30 | 915 | 86 | 9.4 | 958 | 82 | 8.6 | 0.5251 | 0.91 ( 0.68, | 1.22) | 0.90 ( 0.66, | 1.24) | -0.01 (-0.03, | 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6151 |
| <130 | 827 | 84 | 10.2 | 853 | 69 | 8.1 | 0.1408 | 0.80 ( 0.59, | 1.08) | 0.78 ( 0.56, | 1.09) | -0.02 (-0.05, | 0.01) | |
| >=130 | 1174 | 111 | 9.5 | 1199 | 100 | 8.3 | 0.3402 | 0.88 ( 0.68, | 1.14) | 0.87 ( 0.66, | 1.16) | -0.01 (-0.03, | 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3720 |
| <75 | 935 | 99 | 10.6 | 934 | 94 | 10.1 | 0.7097 | 0.95 ( 0.73, | 1.24) | 0.94 ( 0.70, | 1.27) | -0.01 (-0.03, | 0.02) | |
| 75 to <85 | 657 | 65 | 9.9 | 703 | 48 | 6.8 | 0.0407 | 0.69 ( 0.48, | 0.99) | 0.67 ( 0.45, | 0.99) | -0.03 (-0.06, | 0.00) | |
| >=85 | 409 | 31 | 7.6 | 415 | 27 | 6.5 | 0.5470 | 0.86 ( 0.52, | 1.41) | 0.85 ( 0.50, | 1.45) | -0.01 (-0.05, | 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.9889 |
| <30 | 161 | 24 | 14.9 | 148 | 18 | 12.2 | 0.4819 | 0.82 ( 0.46, | 1.44) | 0.79 ( 0.41, | 1.52) | -0.03 (-0.10, 0.05) | |
| 30 to <45 | 550 | 72 | 13.1 | 564 | 63 | 11.2 | 0.3260 | 0.85 ( 0.62, | 1.17) | 0.83 ( 0.58, | 1.20) | -0.02 (-0.06, 0.02) | |
| >=45 | 1289 | 99 | 7.7 | 1340 | 88 | 6.6 | 0.2670 | 0.86 ( 0.65, | 1.13) | 0.84 ( 0.63, | 1.14) | -0.01 (-0.03, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.3767 |
| Normal (<30) | 764 | 75 | 9.8 | 787 | 54 | 6.9 | 0.0351 | 0.70 ( 0.50, | 0.98) | 0.68 ( 0.47, | 0.97) | -0.03 (-0.06, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 77 | 8.4 | 938 | 74 | 7.9 | 0.7099 | 0.94 ( 0.69, | 1.28) | 0.94 ( 0.67, | 1.31) | 0.00 (-0.03, 0.02) | |
| Macroalbuminuria (>300) | 311 | 42 | 13.5 | 318 | 40 | 12.6 | 0.7301 | 0.93 ( 0.62, | 1.39) | 0.92 ( 0.58, | 1.47) | -0.01 (-0.06, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.5378 |
| Low, moderate or high | 1477 | 121 | 8.2 | 1548 | 103 | 6.7 | 0.1062 | 0.81 ( 0.63, | 1.05) | 0.80 ( 0.61, | 1.05) | -0.02 (-0.03, 0.00) | |
| Very high | 519 | 74 | 14.3 | 495 | 65 | 13.1 | 0.6020 | 0.92 ( 0.68, | 1.26) | 0.91 ( 0.64, | 1.30) | -0.01 (-0.05, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.3796 |
| No | 411 | 35 | 8.5 | 410 | 24 | 5.9 | 0.1397 | 0.69 ( 0.42, | 1.13) | 0.67 ( 0.39, | 1.14) | -0.03 (-0.06, 0.01) | |
| Yes | 1590 | 160 | 10.1 | 1642 | 145 | 8.8 | 0.2309 | 0.88 ( 0.71, | 1.09) | 0.87 ( 0.68, | 1.10) | -0.01 (-0.03, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.2411 |
| No | 282 | 31 | 11.0 | 277 | 19 | 6.9 | 0.0869 | 0.62 ( 0.36, | 1.08) | 0.60 ( 0.33, | 1.08) | -0.04 (-0.09, 0.01) | |
| Yes | 1719 | 164 | 9.5 | 1775 | 150 | 8.5 | 0.2602 | 0.89 ( 0.72, | 1.09) | 0.88 ( 0.69, | 1.10) | -0.01 (-0.03, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.1331 |
| No | 229 | 16 | 7.0 | 250 | 23 | 9.2 | 0.3763 | 1.32 ( 0.71, | 2.43) | 1.35 ( 0.69, | 2.62) | 0.02 (-0.03, 0.07) | |
| Yes | 1772 | 179 | 10.1 | 1802 | 146 | 8.1 | 0.0376 | 0.80 ( 0.65, | 0.99) | 0.78 ( 0.62, | 0.99) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 22 | 1.1 | 2052 | 12 | 0.6 | 0.0725 | 0.53 | ( 0.26, 1.07) | 0.53 | ( 0.26, 1.07) | -0.01 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.2173 |
| Male | 1065 | 16 | 1.5 | 1093 | 11 | 1.0 | 0.3001 | 0.67 | ( 0.31, 1.44) | 0.67 | ( 0.31, 1.44) | 0.00 | (-0.01, 0.00) | |
| Female | 936 | 6 | 0.6 | 959 | 1 | 0.1 | 0.0541 | 0.16 | ( 0.02, 1.35) | 0.16 | ( 0.02, 1.35) | -0.01 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.3641 |
| <65 | 331 | 8 | 2.4 | 313 | 6 | 1.9 | 0.6637 | 0.79 | ( 0.28, 2.26) | 0.79 | ( 0.27, 2.30) | 0.00 | (-0.03, 0.02) | |
| >=65 | 1670 | 14 | 0.8 | 1739 | 6 | 0.3 | 0.0594 | 0.41 | ( 0.16, 1.07) | 0.41 | ( 0.16, 1.07) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.9442 |
| North America | 273 | 5 | 1.8 | 273 | 4 | 1.5 | 0.7368 | 0.80 | ( 0.22, 2.95) | 0.80 | ( 0.21, 3.00) | 0.00 | (-0.03, 0.02) | |
| Latin America | 511 | 5 | 1.0 | 504 | 2 | 0.4 | 0.2629 | 0.41 | ( 0.08, 2.08) | 0.40 | ( 0.08, 2.09) | -0.01 | (-0.02, 0.00) | |
| Europe | 865 | 10 | 1.2 | 894 | 5 | 0.6 | 0.1736 | 0.48 | ( 0.17, 1.41) | 0.48 | ( 0.16, 1.41) | -0.01 | (-0.01, 0.00) | |
| Asia | 231 | 1 | 0.4 | 248 | 0 | 0 | 0.4478 | 0.31 | ( 0.01, 7.59) | 0.31 | ( 0.01, 7.63) | 0.00 | (-0.02, 0.01) | |
| Other | 121 | 1 | 0.8 | 133 | 1 | 0.8 | 0.9465 | 0.91 | ( 0.06,14.39) | 0.91 | ( 0.06,14.69) | 0.00 | (-0.02, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9520 |
| Diabetic | 1045 | 20 | 1.9 | 1081 | 11 | 1.0 | 0.0848 | 0.53 | ( 0.26, 1.10) | 0.53 | ( 0.25, 1.11) | -0.01 | (-0.02, 0.00) | |
| Non-Diabetic | 956 | 2 | 0.2 | 971 | 1 | 0.1 | 0.5543 | 0.49 | ( 0.04, 5.42) | 0.49 | ( 0.04, 5.43) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2664 |
| <30 | 1086 | 10 | 0.9 | 1094 | 3 | 0.3 | 0.0499 | 0.30 | ( 0.08, 1.08) | 0.30 | ( 0.08, 1.08) | -0.01 | (-0.01, 0.00) | |
| >=30 | 915 | 12 | 1.3 | 958 | 9 | 0.9 | 0.4447 | 0.72 | ( 0.30, 1.69) | 0.71 | ( 0.30, 1.70) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8490 |
| <130 | 827 | 8 | 1.0 | 853 | 4 | 0.5 | 0.2252 | 0.48 | ( 0.15, 1.60) | 0.48 | ( 0.14, 1.61) | 0.00 | (-0.01, 0.00) | |
| >=130 | 1174 | 14 | 1.2 | 1199 | 8 | 0.7 | 0.1819 | 0.56 | ( 0.24, 1.33) | 0.56 | ( 0.23, 1.33) | -0.01 | (-0.01, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5288 |
| <75 | 935 | 13 | 1.4 | 934 | 6 | 0.6 | 0.1070 | 0.46 | ( 0.18, 1.21) | 0.46 | ( 0.17, 1.21) | -0.01 | (-0.02, 0.00) | |
| 75 to <85 | 657 | 8 | 1.2 | 703 | 4 | 0.6 | 0.2012 | 0.47 | ( 0.14, 1.54) | 0.46 | ( 0.14, 1.55) | -0.01 | (-0.02, 0.00) | |
| >=85 | 409 | 1 | 0.2 | 415 | 2 | 0.5 | 0.5715 | 1.97 | ( 0.18,21.65) | 1.98 | ( 0.18,21.87) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3066 |
| <30 | 161 | 2 | 1.2 | 148 | 3 | 2.0 | 0.5849 | 1.63 | ( 0.28, 9.63) | 1.64 | ( 0.27, 9.98) | 0.01 | (-0.02, 0.04) | |
| 30 to <45 | 550 | 5 | 0.9 | 564 | 1 | 0.2 | 0.0952 | 0.20 | ( 0.02, 1.66) | 0.19 | ( 0.02, 1.66) | -0.01 | (-0.02, 0.00) | |
| >=45 | 1289 | 15 | 1.2 | 1340 | 8 | 0.6 | 0.1188 | 0.51 | ( 0.22, 1.21) | 0.51 | ( 0.22, 1.21) | -0.01 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8651 |
| Normal (<30) | 764 | 4 | 0.5 | 787 | 3 | 0.4 | 0.6758 | 0.73 | ( 0.16, 3.24) | 0.73 | ( 0.16, 3.26) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 7 | 0.8 | 938 | 4 | 0.4 | 0.3484 | 0.56 | ( 0.16, 1.91) | 0.56 | ( 0.16, 1.92) | 0.00 | (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 311 | 11 | 3.5 | 318 | 5 | 1.6 | 0.1177 | 0.44 | ( 0.16, 1.26) | 0.44 | ( 0.15, 1.27) | -0.02 | (-0.04, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4821 |
| Low, moderate or high | 1477 | 15 | 1.0 | 1548 | 7 | 0.5 | 0.0683 | 0.45 | ( 0.18, 1.09) | 0.44 | ( 0.18, 1.09) | -0.01 | (-0.01, 0.00) | |
| Very high | 519 | 7 | 1.3 | 495 | 5 | 1.0 | 0.6182 | 0.75 | ( 0.24, 2.34) | 0.75 | ( 0.24, 2.37) | 0.00 | (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4962 |
| No | 411 | 2 | 0.5 | 410 | 2 | 0.5 | 0.9981 | 1.00 | ( 0.14, 7.08) | 1.00 | ( 0.14, 7.15) | 0.00 | (-0.01, 0.01) | |
| Yes | 1590 | 20 | 1.3 | 1642 | 10 | 0.6 | 0.0545 | 0.48 | ( 0.23, 1.03) | 0.48 | ( 0.22, 1.03) | -0.01 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3317 |
| No | 282 | 5 | 1.8 | 277 | 1 | 0.4 | 0.1053 | 0.20 | ( 0.02, 1.73) | 0.20 | ( 0.02, 1.73) | -0.01 | (-0.03, 0.00) | |
| Yes | 1719 | 17 | 1.0 | 1775 | 11 | 0.6 | 0.2210 | 0.63 | ( 0.29, 1.33) | 0.62 | ( 0.29, 1.34) | 0.00 | (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3161 |
| No | 229 | 3 | 1.3 | 250 | 0 | 0 | 0.1106 | 0.13 | (<0.01, 2.52) | 0.13 | (<0.01, 2.51) | -0.01 | (-0.03, 0.00) | |
| Yes | 1772 | 19 | 1.1 | 1802 | 12 | 0.7 | 0.1903 | 0.62 | ( 0.30, 1.28) | 0.62 | ( 0.30, 1.28) | 0.00 | (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 39 | 1.9 | 2052 | 25 | 1.2 | 0.0621 | 0.63 ( 0.38, 1.03) | 0.62 ( 0.37, 1.03) | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | 0.1306 |
| Male | 1065 | 19 | 1.8 | 1093 | 17 | 1.6 | 0.6784 | 0.87 ( 0.46, 1.67) | 0.87 ( 0.45, 1.68) | 0.00 (-0.01, 0.01) | |
| Female | 936 | 20 | 2.1 | 959 | 8 | 0.8 | 0.0188 | 0.39 ( 0.17, 0.88) | 0.39 ( 0.17, 0.88) | -0.01 (-0.02, 0.00) | |
| Age [years] | | | | | | | | | | | 0.7349 |
| <65 | 331 | 4 | 1.2 | 313 | 3 | 1.0 | 0.7598 | 0.79 ( 0.18, 3.52) | 0.79 ( 0.18, 3.56) | 0.00 (-0.02, 0.01) | |
| >=65 | 1670 | 35 | 2.1 | 1739 | 22 | 1.3 | 0.0586 | 0.60 ( 0.36, 1.02) | 0.60 ( 0.35, 1.02) | -0.01 (-0.02, 0.00) | |
| Region | | | | | | | | | | | 0.2134 |
| North America | 273 | 8 | 2.9 | 273 | 6 | 2.2 | 0.5882 | 0.75 ( 0.26, 2.13) | 0.74 ( 0.25, 2.17) | -0.01 (-0.03, 0.02) | |
| Latin America | 511 | 5 | 1.0 | 504 | 8 | 1.6 | 0.3884 | 1.62 ( 0.53, 4.93) | 1.63 ( 0.53, 5.02) | 0.01 (-0.01, 0.02) | |
| Europe | 865 | 18 | 2.1 | 894 | 5 | 0.6 | 0.0050 | 0.27 ( 0.10, 0.72) | 0.26 ( 0.10, 0.72) | -0.02 (-0.03, 0.00) | |
| Asia | 231 | 7 | 3.0 | 248 | 5 | 2.0 | 0.4779 | 0.67 ( 0.21, 2.07) | 0.66 ( 0.21, 2.10) | -0.01 (-0.04, 0.02) | |
| Other | 121 | 1 | 0.8 | 133 | 1 | 0.8 | 0.9465 | 0.91 ( 0.06,14.39) | 0.91 ( 0.06,14.69) | 0.00 (-0.02, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.9836 |
| Diabetic | 1045 | 20 | 1.9 | 1081 | 13 | 1.2 | 0.1847 | 0.63 ( 0.31, 1.26) | 0.62 ( 0.31, 1.26) | -0.01 (-0.02, 0.00) | |
| Non-Diabetic | 956 | 19 | 2.0 | 971 | 12 | 1.2 | 0.1898 | 0.62 ( 0.30, 1.27) | 0.62 ( 0.30, 1.28) | -0.01 (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.4698 |
| <30 | 1086 | 30 | 2.8 | 1094 | 17 | 1.6 | 0.0521 | 0.56 ( 0.31, 1.01) | 0.56 ( 0.30, 1.01) | -0.01 (-0.02, 0.00) | |
| >=30 | 915 | 9 | 1.0 | 958 | 8 | 0.8 | 0.7347 | 0.85 ( 0.33, 2.19) | 0.85 ( 0.33, 2.21) | 0.00 (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.7979 |
| <130 | 827 | 23 | 2.8 | 853 | 14 | 1.6 | 0.1115 | 0.59 ( 0.31, 1.14) | 0.58 ( 0.30, 1.14) | -0.01 (-0.03, 0.00) | |
| >=130 | 1174 | 16 | 1.4 | 1199 | 11 | 0.9 | 0.3064 | 0.67 ( 0.31, 1.44) | 0.67 ( 0.31, 1.45) | 0.00 (-0.01, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.7300 |
| <75 | 935 | 27 | 2.9 | 934 | 16 | 1.7 | 0.0903 | 0.59 ( 0.32, 1.09) | 0.59 ( 0.31, 1.10) | -0.01 (-0.03, 0.00) | |
| 75 to <85 | 657 | 6 | 0.9 | 703 | 6 | 0.9 | 0.9063 | 0.93 ( 0.30, 2.88) | 0.93 ( 0.30, 2.91) | 0.00 (-0.01, 0.01) | |
| >=85 | 409 | 6 | 1.5 | 415 | 3 | 0.7 | 0.3042 | 0.49 ( 0.12, 1.96) | 0.49 ( 0.12, 1.97) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4880 |
| <30 | 161 | 5 | 3.1 | 148 | 5 | 3.4 | 0.8923 | 1.09 | ( 0.32, 3.68) | 1.09 | ( 0.31, 3.85) | 0.00 | (-0.04, 0.04) | |
| 30 to <45 | 550 | 10 | 1.8 | 564 | 4 | 0.7 | 0.0967 | 0.39 | ( 0.12, 1.24) | 0.39 | ( 0.12, 1.24) | -0.01 | (-0.02, 0.00) | |
| >=45 | 1289 | 24 | 1.9 | 1340 | 16 | 1.2 | 0.1620 | 0.64 | ( 0.34, 1.20) | 0.64 | ( 0.34, 1.20) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1556 |
| Normal (<30) | 764 | 17 | 2.2 | 787 | 6 | 0.8 | 0.0172 | 0.34 | ( 0.14, 0.86) | 0.34 | ( 0.13, 0.86) | -0.01 | (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 21 | 2.3 | 938 | 16 | 1.7 | 0.3753 | 0.75 | ( 0.39, 1.42) | 0.74 | ( 0.39, 1.43) | -0.01 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 311 | 1 | 0.3 | 318 | 3 | 0.9 | 0.3266 | 2.93 | ( 0.31,28.05) | 2.95 | ( 0.31,28.54) | 0.01 | (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7078 |
| Low, moderate or high | 1477 | 29 | 2.0 | 1548 | 18 | 1.2 | 0.0751 | 0.59 | ( 0.33, 1.06) | 0.59 | ( 0.32, 1.06) | -0.01 | (-0.02, 0.00) | |
| Very high | 519 | 10 | 1.9 | 495 | 7 | 1.4 | 0.5251 | 0.73 | ( 0.28, 1.91) | 0.73 | ( 0.28, 1.93) | -0.01 | (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4585 |
| No | 411 | 13 | 3.2 | 410 | 6 | 1.5 | 0.1054 | 0.46 | ( 0.18, 1.21) | 0.45 | ( 0.17, 1.21) | -0.02 | (-0.04, 0.00) | |
| Yes | 1590 | 26 | 1.6 | 1642 | 19 | 1.2 | 0.2462 | 0.71 | ( 0.39, 1.27) | 0.70 | ( 0.39, 1.28) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6579 |
| No | 282 | 10 | 3.5 | 277 | 5 | 1.8 | 0.2028 | 0.51 | ( 0.18, 1.47) | 0.50 | ( 0.17, 1.48) | -0.02 | (-0.04, 0.01) | |
| Yes | 1719 | 29 | 1.7 | 1775 | 20 | 1.1 | 0.1591 | 0.67 | ( 0.38, 1.18) | 0.66 | ( 0.37, 1.18) | -0.01 | (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2010 |
| No | 229 | 4 | 1.7 | 250 | 0 | 0 | 0.0577 | 0.10 | (<0.01, 1.88) | 0.10 | (<0.01, 1.87) | -0.02 | (-0.04, 0.00) | |
| Yes | 1772 | 35 | 2.0 | 1802 | 25 | 1.4 | 0.1714 | 0.70 | ( 0.42, 1.17) | 0.70 | ( 0.42, 1.17) | -0.01 | (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 5 | 0.2 | 2052 | 6 | 0.3 | 0.7947 | 1.17 ( 0.36, 3.83) | 1.17 ( 0.36, 3.84) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 1065 | 2 | 0.2 | 1093 | 3 | 0.3 | | | | | |
| Female | 936 | 3 | 0.3 | 959 | 3 | 0.3 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 331 | 5 | 1.5 | 313 | 1 | 0.3 | | | | | |
| >=65 | 1670 | 0 | 0 | 1739 | 5 | 0.3 | | | | | |
| Region | | | | | | | | | | | |
| North America | 273 | 1 | 0.4 | 273 | 3 | 1.1 | | | | | |
| Latin America | 511 | 1 | 0.2 | 504 | 0 | 0 | | | | | |
| Europe | 865 | 0 | 0 | 894 | 1 | 0.1 | | | | | |
| Asia | 231 | 1 | 0.4 | 248 | 0 | 0 | | | | | |
| Other | 121 | 2 | 1.7 | 133 | 2 | 1.5 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | 0.9374 |
| Diabetic | 1045 | 5 | 0.5 | 1081 | 6 | 0.6 | 0.8057 | 1.16 ( 0.36, 3.79) | 1.16 ( 0.35, 3.82) | 0.00 (-0.01, 0.01) | |
| Non-Diabetic | 956 | 0 | 0 | 971 | 0 | 0 | 0.9938 | 0.98 ( 0.02,49.57) | 0.98 ( 0.02,49.67) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 1086 | 2 | 0.2 | 1094 | 2 | 0.2 | | | | | |
| >=30 | 915 | 3 | 0.3 | 958 | 4 | 0.4 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 827 | 2 | 0.2 | 853 | 1 | 0.1 | | | | | |
| >=130 | 1174 | 3 | 0.3 | 1199 | 5 | 0.4 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 935 | 1 | 0.1 | 934 | 3 | 0.3 | | | | | |
| 75 to <85 | 657 | 2 | 0.3 | 703 | 3 | 0.4 | | | | | |
| >=85 | 409 | 2 | 0.5 | 415 | 0 | 0 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 161 | 2 | 1.2 | 148 | 1 | 0.7 | | | | | |
| 30 to <45 | 550 | 1 | 0.2 | 564 | 2 | 0.4 | | | | | |
| >=45 | 1289 | 2 | 0.2 | 1340 | 3 | 0.2 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 764 | 1 | 0.1 | 787 | 1 | 0.1 | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 3 | 0.3 | 938 | 2 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 311 | 1 | 0.3 | 318 | 3 | 0.9 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1477 | 3 | 0.2 | 1548 | 4 | 0.3 | | | | | |
| Very high | 519 | 2 | 0.4 | 495 | 2 | 0.4 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 411 | 2 | 0.5 | 410 | 1 | 0.2 | | | | | |
| Yes | 1590 | 3 | 0.2 | 1642 | 5 | 0.3 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 282 | 0 | 0 | 277 | 2 | 0.7 | | | | | |
| Yes | 1719 | 5 | 0.3 | 1775 | 4 | 0.2 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 229 | 1 | 0.4 | 250 | 2 | 0.8 | | | | | |
| Yes | 1772 | 4 | 0.2 | 1802 | 4 | 0.2 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 11 | 0.5 | 2052 | 13 | 0.6 | 0.7281 | 1.15 | ( 0.52, 2.57) | 1.15 | ( 0.52, 2.58) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0999 |
| Male | 1065 | 8 | 0.8 | 1093 | 5 | 0.5 | 0.3780 | 0.61 | ( 0.20, 1.86) | 0.61 | ( 0.20, 1.86) | 0.00 | (-0.01, 0.00) | |
| Female | 936 | 3 | 0.3 | 959 | 8 | 0.8 | 0.1411 | 2.60 | ( 0.69, 9.78) | 2.62 | ( 0.69, 9.89) | 0.01 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3333 |
| <65 | 331 | 1 | 0.3 | 313 | 3 | 1.0 | 0.2893 | 3.17 | ( 0.33,30.34) | 3.19 | ( 0.33,30.86) | 0.01 | (-0.01, 0.02) | |
| >=65 | 1670 | 10 | 0.6 | 1739 | 10 | 0.6 | 0.9276 | 0.96 | ( 0.40, 2.30) | 0.96 | ( 0.40, 2.31) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | |
| North America | 273 | 1 | 0.4 | 273 | 5 | 1.8 | | | | | | | | |
| Latin America | 511 | 3 | 0.6 | 504 | 2 | 0.4 | | | | | | | | |
| Europe | 865 | 6 | 0.7 | 894 | 2 | 0.2 | | | | | | | | |
| Asia | 231 | 0 | 0 | 248 | 1 | 0.4 | | | | | | | | |
| Other | 121 | 1 | 0.8 | 133 | 3 | 2.3 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9419 |
| Diabetic | 1045 | 11 | 1.1 | 1081 | 13 | 1.2 | 0.7435 | 1.14 | ( 0.51, 2.54) | 1.14 | ( 0.51, 2.57) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 956 | 0 | 0 | 971 | 0 | 0 | 0.9938 | 0.98 | ( 0.02,49.57) | 0.98 | ( 0.02,49.67) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4571 |
| <30 | 1086 | 2 | 0.2 | 1094 | 4 | 0.4 | 0.4187 | 1.99 | ( 0.36,10.82) | 1.99 | ( 0.36,10.88) | 0.00 | ( 0.00, 0.01) | |
| >=30 | 915 | 9 | 1.0 | 958 | 9 | 0.9 | 0.9220 | 0.96 | ( 0.38, 2.40) | 0.95 | ( 0.38, 2.42) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9822 |
| <130 | 827 | 5 | 0.6 | 853 | 6 | 0.7 | 0.8018 | 1.16 | ( 0.36, 3.80) | 1.16 | ( 0.35, 3.83) | 0.00 | (-0.01, 0.01) | |
| >=130 | 1174 | 6 | 0.5 | 1199 | 7 | 0.6 | 0.8103 | 1.14 | ( 0.39, 3.39) | 1.14 | ( 0.38, 3.41) | 0.00 | (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5188 |
| <75 | 935 | 7 | 0.7 | 934 | 5 | 0.5 | 0.5637 | 0.72 | ( 0.23, 2.24) | 0.71 | ( 0.23, 2.26) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 657 | 4 | 0.6 | 703 | 7 | 1.0 | 0.4260 | 1.64 | ( 0.48, 5.56) | 1.64 | ( 0.48, 5.63) | 0.00 | (-0.01, 0.01) | |
| >=85 | 409 | 0 | 0 | 415 | 1 | 0.2 | 0.4854 | 2.96 | ( 0.12,72.37) | 2.96 | ( 0.12,72.97) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1243 |
| <30 | 161 | 1 | 0.6 | 148 | 3 | 2.0 | 0.2747 | 3.26 | ( 0.34,31.03) | 3.31 | ( 0.34,32.18) | 0.01 | (-0.01, 0.04) | |
| 30 to <45 | 550 | 2 | 0.4 | 564 | 6 | 1.1 | 0.1664 | 2.93 | ( 0.59,14.43) | 2.95 | ( 0.59,14.66) | 0.01 | ( 0.00, 0.02) | |
| >=45 | 1289 | 8 | 0.6 | 1340 | 4 | 0.3 | 0.2206 | 0.48 | ( 0.15, 1.59) | 0.48 | ( 0.14, 1.60) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3633 |
| Normal (<30) | 764 | 3 | 0.4 | 787 | 1 | 0.1 | 0.3025 | 0.32 | ( 0.03, 3.10) | 0.32 | ( 0.03, 3.11) | 0.00 | (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 4 | 0.4 | 938 | 8 | 0.9 | 0.2599 | 1.96 | ( 0.59, 6.50) | 1.97 | ( 0.59, 6.57) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 311 | 4 | 1.3 | 318 | 4 | 1.3 | 0.9747 | 0.98 | ( 0.25, 3.88) | 0.98 | ( 0.24, 3.94) | 0.00 | (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3951 |
| Low, moderate or high | 1477 | 5 | 0.3 | 1548 | 4 | 0.3 | 0.6859 | 0.76 | ( 0.21, 2.84) | 0.76 | ( 0.20, 2.85) | 0.00 | ( 0.00, 0.00) | |
| Very high | 519 | 6 | 1.2 | 495 | 9 | 1.8 | 0.3827 | 1.57 | ( 0.56, 4.39) | 1.58 | ( 0.56, 4.48) | 0.01 | (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2678 |
| No | 411 | 2 | 0.5 | 410 | 5 | 1.2 | 0.2535 | 2.51 | ( 0.49,12.84) | 2.52 | ( 0.49,13.09) | 0.01 | (-0.01, 0.02) | |
| Yes | 1590 | 9 | 0.6 | 1642 | 8 | 0.5 | 0.7568 | 0.86 | ( 0.33, 2.23) | 0.86 | ( 0.33, 2.23) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9285 |
| No | 282 | 1 | 0.4 | 277 | 1 | 0.4 | 0.9899 | 1.02 | ( 0.06,16.20) | 1.02 | ( 0.06,16.36) | 0.00 | (-0.01, 0.01) | |
| Yes | 1719 | 10 | 0.6 | 1775 | 12 | 0.7 | 0.7246 | 1.16 | ( 0.50, 2.68) | 1.16 | ( 0.50, 2.70) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8636 |
| No | 229 | 1 | 0.4 | 250 | 1 | 0.4 | 0.9504 | 0.92 | ( 0.06,14.56) | 0.92 | ( 0.06,14.72) | 0.00 | (-0.01, 0.01) | |
| Yes | 1772 | 10 | 0.6 | 1802 | 12 | 0.7 | 0.6978 | 1.18 | ( 0.51, 2.72) | 1.18 | ( 0.51, 2.74) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 45 | 2.2 | 2052 | 59 | 2.9 | 0.2074 | 1.28 | ( 0.87, 1.88) | 1.29 | ( 0.87, 1.91) | 0.01 | ( 0.00, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.0209 |
| Male | 1065 | 27 | 2.5 | 1093 | 22 | 2.0 | 0.4154 | 0.79 | ( 0.46, 1.39) | 0.79 | ( 0.45, 1.40) | -0.01 | (-0.02, 0.01) | |
| Female | 936 | 18 | 1.9 | 959 | 37 | 3.9 | 0.0121 | 2.01 | ( 1.15, 3.50) | 2.05 | ( 1.16, 3.62) | 0.02 | ( 0.00, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.4465 |
| <65 | 331 | 3 | 0.9 | 313 | 6 | 1.9 | 0.2749 | 2.12 | ( 0.53, 8.38) | 2.14 | ( 0.53, 8.62) | 0.01 | (-0.01, 0.03) | |
| >=65 | 1670 | 42 | 2.5 | 1739 | 53 | 3.0 | 0.3448 | 1.21 | ( 0.81, 1.81) | 1.22 | ( 0.81, 1.84) | 0.01 | (-0.01, 0.02) | |
| Region | | | | | | | | | | | | | | 0.8644 |
| North America | 273 | 10 | 3.7 | 273 | 11 | 4.0 | 0.8239 | 1.10 | ( 0.47, 2.55) | 1.10 | ( 0.46, 2.64) | 0.00 | (-0.03, 0.04) | |
| Latin America | 511 | 12 | 2.3 | 504 | 19 | 3.8 | 0.1882 | 1.61 | ( 0.79, 3.27) | 1.63 | ( 0.78, 3.39) | 0.01 | (-0.01, 0.04) | |
| Europe | 865 | 17 | 2.0 | 894 | 18 | 2.0 | 0.9424 | 1.02 | ( 0.53, 1.97) | 1.02 | ( 0.52, 2.00) | 0.00 | (-0.01, 0.01) | |
| Asia | 231 | 3 | 1.3 | 248 | 5 | 2.0 | 0.5404 | 1.55 | ( 0.38, 6.42) | 1.56 | ( 0.37, 6.62) | 0.01 | (-0.02, 0.03) | |
| Other | 121 | 3 | 2.5 | 133 | 6 | 4.5 | 0.3816 | 1.82 | ( 0.47, 7.12) | 1.86 | ( 0.45, 7.60) | 0.02 | (-0.02, 0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7219 |
| Diabetic | 1045 | 25 | 2.4 | 1081 | 31 | 2.9 | 0.4938 | 1.20 | ( 0.71, 2.02) | 1.20 | ( 0.71, 2.05) | 0.00 | (-0.01, 0.02) | |
| Non-Diabetic | 956 | 20 | 2.1 | 971 | 28 | 2.9 | 0.2649 | 1.38 | ( 0.78, 2.43) | 1.39 | ( 0.78, 2.48) | 0.01 | (-0.01, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1001 |
| <30 | 1086 | 26 | 2.4 | 1094 | 24 | 2.2 | 0.7547 | 0.92 | ( 0.53, 1.59) | 0.91 | ( 0.52, 1.60) | 0.00 | (-0.01, 0.01) | |
| >=30 | 915 | 19 | 2.1 | 958 | 35 | 3.7 | 0.0415 | 1.76 | ( 1.01, 3.05) | 1.79 | ( 1.02, 3.15) | 0.02 | ( 0.00, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1099 |
| <130 | 827 | 18 | 2.2 | 853 | 33 | 3.9 | 0.0433 | 1.78 | ( 1.01, 3.13) | 1.81 | ( 1.01, 3.24) | 0.02 | ( 0.00, 0.03) | |
| >=130 | 1174 | 27 | 2.3 | 1199 | 26 | 2.2 | 0.8286 | 0.94 | ( 0.55, 1.61) | 0.94 | ( 0.55, 1.62) | 0.00 | (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3865 |
| <75 | 935 | 20 | 2.1 | 934 | 30 | 3.2 | 0.1506 | 1.50 | ( 0.86, 2.62) | 1.52 | ( 0.86, 2.69) | 0.01 | ( 0.00, 0.03) | |
| 75 to <85 | 657 | 18 | 2.7 | 703 | 17 | 2.4 | 0.7083 | 0.88 | ( 0.46, 1.70) | 0.88 | ( 0.45, 1.72) | 0.00 | (-0.02, 0.01) | |
| >=85 | 409 | 7 | 1.7 | 415 | 12 | 2.9 | 0.2591 | 1.69 | ( 0.67, 4.25) | 1.71 | ( 0.67, 4.39) | 0.01 | (-0.01, 0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3027 |
| <30 | 161 | 8 | 5.0 | 148 | 4 | 2.7 | 0.3030 | 0.54 | ( 0.17, 1.77) | 0.53 | ( 0.16, 1.80) | -0.02 | (-0.07, 0.02) | |
| 30 to <45 | 550 | 16 | 2.9 | 564 | 25 | 4.4 | 0.1769 | 1.52 | ( 0.82, 2.82) | 1.55 | ( 0.82, 2.93) | 0.02 | (-0.01, 0.04) | |
| >=45 | 1289 | 21 | 1.6 | 1340 | 30 | 2.2 | 0.2572 | 1.37 | ( 0.79, 2.39) | 1.38 | ( 0.79, 2.43) | 0.01 | ( 0.00, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6266 |
| Normal (<30) | 764 | 15 | 2.0 | 787 | 25 | 3.2 | 0.1318 | 1.62 | ( 0.86, 3.04) | 1.64 | ( 0.86, 3.13) | 0.01 | ( 0.00, 0.03) | |
| Microalbuminuria (30 to <=300) | 921 | 23 | 2.5 | 938 | 25 | 2.7 | 0.8194 | 1.07 | ( 0.61, 1.87) | 1.07 | ( 0.60, 1.90) | 0.00 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 311 | 7 | 2.3 | 318 | 9 | 2.8 | 0.6445 | 1.26 | ( 0.47, 3.33) | 1.26 | ( 0.47, 3.44) | 0.01 | (-0.02, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5178 |
| Low, moderate or high | 1477 | 26 | 1.8 | 1548 | 39 | 2.5 | 0.1501 | 1.43 | ( 0.88, 2.34) | 1.44 | ( 0.87, 2.38) | 0.01 | ( 0.00, 0.02) | |
| Very high | 519 | 19 | 3.7 | 495 | 20 | 4.0 | 0.7534 | 1.10 | ( 0.60, 2.04) | 1.11 | ( 0.58, 2.10) | 0.00 | (-0.02, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3022 |
| No | 411 | 10 | 2.4 | 410 | 18 | 4.4 | 0.1224 | 1.80 | ( 0.84, 3.86) | 1.84 | ( 0.84, 4.04) | 0.02 | (-0.01, 0.04) | |
| Yes | 1590 | 35 | 2.2 | 1642 | 41 | 2.5 | 0.5792 | 1.13 | ( 0.73, 1.77) | 1.14 | ( 0.72, 1.80) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8836 |
| No | 282 | 9 | 3.2 | 277 | 12 | 4.3 | 0.4783 | 1.36 | ( 0.58, 3.17) | 1.37 | ( 0.57, 3.31) | 0.01 | (-0.02, 0.04) | |
| Yes | 1719 | 36 | 2.1 | 1775 | 47 | 2.6 | 0.2827 | 1.26 | ( 0.82, 1.94) | 1.27 | ( 0.82, 1.97) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5937 |
| No | 229 | 3 | 1.3 | 250 | 6 | 2.4 | 0.3802 | 1.83 | ( 0.46, 7.24) | 1.85 | ( 0.46, 7.49) | 0.01 | (-0.01, 0.03) | |
| Yes | 1772 | 42 | 2.4 | 1802 | 53 | 2.9 | 0.2887 | 1.24 | ( 0.83, 1.85) | 1.25 | ( 0.83, 1.88) | 0.01 | ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 2001 | 8 | 0.4 | 2052 | 1 | <0.1 | 0.0176 | 0.12 ( 0.02, 0.97) | 0.12 ( 0.02, 0.97) | 0.00 (-0.01, 0.00) | | |
| Sex | | | | | | | | | | | | |
| Male | 1065 | 7 | 0.7 | 1093 | 1 | 0.1 | | | | | | |
| Female | 936 | 1 | 0.1 | 959 | 0 | 0 | | | | | | |
| Age [years] | | | | | | | | | | | | |
| <65 | 331 | 1 | 0.3 | 313 | 0 | 0 | | | | | | |
| >=65 | 1670 | 7 | 0.4 | 1739 | 1 | 0.1 | | | | | | |
| Region | | | | | | | | | | | | |
| North America | 273 | 2 | 0.7 | 273 | 0 | 0 | | | | | | |
| Latin America | 511 | 2 | 0.4 | 504 | 0 | 0 | | | | | | |
| Europe | 865 | 2 | 0.2 | 894 | 1 | 0.1 | | | | | | |
| Asia | 231 | 2 | 0.9 | 248 | 0 | 0 | | | | | | |
| Other | 121 | 0 | 0 | 133 | 0 | 0 | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | |
| Diabetic | 1045 | 6 | 0.6 | 1081 | 1 | 0.1 | | | | | | |
| Non-Diabetic | 956 | 2 | 0.2 | 971 | 0 | 0 | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | |
| <30 | 1086 | 5 | 0.5 | 1094 | 1 | 0.1 | | | | | | |
| >=30 | 915 | 3 | 0.3 | 958 | 0 | 0 | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 827 | 6 | 0.7 | 853 | 0 | 0 | | | | | | |
| >=130 | 1174 | 2 | 0.2 | 1199 | 1 | 0.1 | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 935 | 6 | 0.6 | 934 | 1 | 0.1 | | | | | | |
| 75 to <85 | 657 | 2 | 0.3 | 703 | 0 | 0 | | | | | | |
| >=85 | 409 | 0 | 0 | 415 | 0 | 0 | | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 161 | 1 | 0.6 | 148 | 0 | 0 | | | | | |
| 30 to <45 | 550 | 3 | 0.5 | 564 | 1 | 0.2 | | | | | |
| >=45 | 1289 | 4 | 0.3 | 1340 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 764 | 1 | 0.1 | 787 | 1 | 0.1 | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 5 | 0.5 | 938 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 311 | 2 | 0.6 | 318 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1477 | 5 | 0.3 | 1548 | 1 | 0.1 | | | | | |
| Very high | 519 | 3 | 0.6 | 495 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 411 | 4 | 1.0 | 410 | 0 | 0 | | | | | |
| Yes | 1590 | 4 | 0.3 | 1642 | 1 | 0.1 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 282 | 0 | 0 | 277 | 0 | 0 | | | | | |
| Yes | 1719 | 8 | 0.5 | 1775 | 1 | 0.1 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 229 | 0 | 0 | 250 | 0 | 0 | | | | | |
| Yes | 1772 | 8 | 0.5 | 1802 | 1 | 0.1 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 16 | 0.8 | 2052 | 24 | 1.2 | 0.2335 | 1.46 | ( 0.78, 2.75) | 1.47 | ( 0.78, 2.77) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.3639 |
| Male | 1065 | 9 | 0.8 | 1093 | 10 | 0.9 | 0.8621 | 1.08 | ( 0.44, 2.65) | 1.08 | ( 0.44, 2.68) | 0.00 | (-0.01, 0.01) | |
| Female | 936 | 7 | 0.7 | 959 | 14 | 1.5 | 0.1388 | 1.95 | ( 0.79, 4.81) | 1.97 | ( 0.79, 4.89) | 0.01 | ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.8194 |
| <65 | 331 | 1 | 0.3 | 313 | 1 | 0.3 | 0.9684 | 1.06 | ( 0.07,16.83) | 1.06 | ( 0.07,16.98) | 0.00 | (-0.01, 0.01) | |
| >=65 | 1670 | 15 | 0.9 | 1739 | 23 | 1.3 | 0.2381 | 1.47 | ( 0.77, 2.81) | 1.48 | ( 0.77, 2.84) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.7010 |
| North America | 273 | 2 | 0.7 | 273 | 4 | 1.5 | 0.4116 | 2.00 | ( 0.37,10.83) | 2.01 | ( 0.37,11.09) | 0.01 | (-0.01, 0.02) | |
| Latin America | 511 | 3 | 0.6 | 504 | 5 | 1.0 | 0.4657 | 1.69 | ( 0.41, 7.03) | 1.70 | ( 0.40, 7.14) | 0.00 | (-0.01, 0.01) | |
| Europe | 865 | 8 | 0.9 | 894 | 8 | 0.9 | 0.9472 | 0.97 | ( 0.36, 2.57) | 0.97 | ( 0.36, 2.59) | 0.00 | (-0.01, 0.01) | |
| Asia | 231 | 1 | 0.4 | 248 | 5 | 2.0 | 0.1195 | 4.66 | ( 0.55,39.57) | 4.73 | ( 0.55,40.81) | 0.02 | ( 0.00, 0.04) | |
| Other | 121 | 2 | 1.7 | 133 | 2 | 1.5 | 0.9240 | 0.91 | ( 0.13, 6.36) | 0.91 | ( 0.13, 6.55) | 0.00 | (-0.03, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4493 |
| Diabetic | 1045 | 8 | 0.8 | 1081 | 15 | 1.4 | 0.1657 | 1.81 | ( 0.77, 4.26) | 1.82 | ( 0.77, 4.32) | 0.01 | ( 0.00, 0.01) | |
| Non-Diabetic | 956 | 8 | 0.8 | 971 | 9 | 0.9 | 0.8326 | 1.11 | ( 0.43, 2.86) | 1.11 | ( 0.43, 2.89) | 0.00 | (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0485 |
| <30 | 1086 | 12 | 1.1 | 1094 | 10 | 0.9 | 0.6557 | 0.83 | ( 0.36, 1.91) | 0.83 | ( 0.36, 1.92) | 0.00 | (-0.01, 0.01) | |
| >=30 | 915 | 4 | 0.4 | 958 | 14 | 1.5 | 0.0231 | 3.34 | ( 1.10,10.12) | 3.38 | ( 1.11,10.30) | 0.01 | ( 0.00, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6857 |
| <130 | 827 | 9 | 1.1 | 853 | 12 | 1.4 | 0.5569 | 1.29 | ( 0.55, 3.05) | 1.30 | ( 0.54, 3.09) | 0.00 | (-0.01, 0.01) | |
| >=130 | 1174 | 7 | 0.6 | 1199 | 12 | 1.0 | 0.2689 | 1.68 | ( 0.66, 4.25) | 1.69 | ( 0.66, 4.30) | 0.00 | ( 0.00, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5838 |
| <75 | 935 | 8 | 0.9 | 934 | 8 | 0.9 | 0.9983 | 1.00 | ( 0.38, 2.66) | 1.00 | ( 0.37, 2.68) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 657 | 5 | 0.8 | 703 | 9 | 1.3 | 0.3432 | 1.68 | ( 0.57, 4.99) | 1.69 | ( 0.56, 5.07) | 0.01 | (-0.01, 0.02) | |
| >=85 | 409 | 3 | 0.7 | 415 | 7 | 1.7 | 0.2115 | 2.30 | ( 0.60, 8.83) | 2.32 | ( 0.60, 9.04) | 0.01 | (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6513 |
| <30 | 161 | 4 | 2.5 | 148 | 3 | 2.0 | 0.7872 | 0.82 | ( 0.19, 3.58) | 0.81 | ( 0.18, 3.69) | 0.00 | (-0.04, 0.03) | |
| 30 to <45 | 550 | 7 | 1.3 | 564 | 11 | 2.0 | 0.3698 | 1.53 | ( 0.60, 3.92) | 1.54 | ( 0.59, 4.01) | 0.01 | (-0.01, 0.02) | |
| >=45 | 1289 | 5 | 0.4 | 1340 | 10 | 0.7 | 0.2226 | 1.92 | ( 0.66, 5.61) | 1.93 | ( 0.66, 5.66) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9292 |
| Normal (<30) | 764 | 6 | 0.8 | 787 | 10 | 1.3 | 0.3443 | 1.62 | ( 0.59, 4.43) | 1.63 | ( 0.59, 4.50) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 7 | 0.8 | 938 | 9 | 1.0 | 0.6416 | 1.26 | ( 0.47, 3.38) | 1.26 | ( 0.47, 3.41) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 311 | 3 | 1.0 | 318 | 5 | 1.6 | 0.4965 | 1.63 | ( 0.39, 6.76) | 1.64 | ( 0.39, 6.92) | 0.01 | (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8075 |
| Low, moderate or high | 1477 | 7 | 0.5 | 1548 | 12 | 0.8 | 0.2945 | 1.64 | ( 0.65, 4.14) | 1.64 | ( 0.64, 4.18) | 0.00 | ( 0.00, 0.01) | |
| Very high | 519 | 9 | 1.7 | 495 | 12 | 2.4 | 0.4405 | 1.40 | ( 0.59, 3.29) | 1.41 | ( 0.59, 3.37) | 0.01 | (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2119 |
| No | 411 | 2 | 0.5 | 410 | 7 | 1.7 | 0.0930 | 3.51 | ( 0.73,16.79) | 3.55 | ( 0.73,17.20) | 0.01 | ( 0.00, 0.03) | |
| Yes | 1590 | 14 | 0.9 | 1642 | 17 | 1.0 | 0.6517 | 1.18 | ( 0.58, 2.38) | 1.18 | ( 0.58, 2.40) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3113 |
| No | 282 | 2 | 0.7 | 277 | 6 | 2.2 | 0.1471 | 3.05 | ( 0.62,15.00) | 3.10 | ( 0.62,15.49) | 0.01 | (-0.01, 0.03) | |
| Yes | 1719 | 14 | 0.8 | 1775 | 18 | 1.0 | 0.5357 | 1.25 | ( 0.62, 2.50) | 1.25 | ( 0.62, 2.52) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3198 |
| No | 229 | 2 | 0.9 | 250 | 1 | 0.4 | 0.5118 | 0.46 | ( 0.04, 5.02) | 0.46 | ( 0.04, 5.06) | 0.00 | (-0.02, 0.01) | |
| Yes | 1772 | 14 | 0.8 | 1802 | 23 | 1.3 | 0.1510 | 1.62 | ( 0.83, 3.13) | 1.62 | ( 0.83, 3.17) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 55 | 2.7 | 2052 | 63 | 3.1 | 0.5427 | 1.12 | ( 0.78, 1.60) | 1.12 | ( 0.78, 1.62) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.4331 |
| Male | 1065 | 23 | 2.2 | 1093 | 22 | 2.0 | 0.8114 | 0.93 | ( 0.52, 1.66) | 0.93 | ( 0.52, 1.68) | 0.00 | (-0.01, 0.01) | |
| Female | 936 | 32 | 3.4 | 959 | 41 | 4.3 | 0.3328 | 1.25 | ( 0.79, 1.97) | 1.26 | ( 0.79, 2.02) | 0.01 | (-0.01, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.4824 |
| <65 | 331 | 7 | 2.1 | 313 | 5 | 1.6 | 0.6275 | 0.76 | ( 0.24, 2.36) | 0.75 | ( 0.24, 2.39) | -0.01 | (-0.03, 0.02) | |
| >=65 | 1670 | 48 | 2.9 | 1739 | 58 | 3.3 | 0.4382 | 1.16 | ( 0.80, 1.69) | 1.17 | ( 0.79, 1.72) | 0.00 | (-0.01, 0.02) | |
| Region | | | | | | | | | | | | | | 0.7563 |
| North America | 273 | 14 | 5.1 | 273 | 11 | 4.0 | 0.5391 | 0.79 | ( 0.36, 1.70) | 0.78 | ( 0.35, 1.74) | -0.01 | (-0.05, 0.02) | |
| Latin America | 511 | 8 | 1.6 | 504 | 7 | 1.4 | 0.8156 | 0.89 | ( 0.32, 2.43) | 0.89 | ( 0.32, 2.46) | 0.00 | (-0.02, 0.01) | |
| Europe | 865 | 21 | 2.4 | 894 | 25 | 2.8 | 0.6281 | 1.15 | ( 0.65, 2.04) | 1.16 | ( 0.64, 2.08) | 0.00 | (-0.01, 0.02) | |
| Asia | 231 | 9 | 3.9 | 248 | 14 | 5.6 | 0.3710 | 1.45 | ( 0.64, 3.28) | 1.48 | ( 0.63, 3.48) | 0.02 | (-0.02, 0.06) | |
| Other | 121 | 3 | 2.5 | 133 | 6 | 4.5 | 0.3816 | 1.82 | ( 0.47, 7.12) | 1.86 | ( 0.45, 7.60) | 0.02 | (-0.02, 0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0431 |
| Diabetic | 1045 | 21 | 2.0 | 1081 | 36 | 3.3 | 0.0595 | 1.66 | ( 0.97, 2.82) | 1.68 | ( 0.97, 2.90) | 0.01 | ( 0.00, 0.03) | |
| Non-Diabetic | 956 | 34 | 3.6 | 971 | 27 | 2.8 | 0.3308 | 0.78 | ( 0.48, 1.29) | 0.78 | ( 0.46, 1.30) | -0.01 | (-0.02, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7315 |
| <30 | 1086 | 32 | 2.9 | 1094 | 38 | 3.5 | 0.4853 | 1.18 | ( 0.74, 1.87) | 1.19 | ( 0.73, 1.91) | 0.01 | (-0.01, 0.02) | |
| >=30 | 915 | 23 | 2.5 | 958 | 25 | 2.6 | 0.8955 | 1.04 | ( 0.59, 1.82) | 1.04 | ( 0.59, 1.84) | 0.00 | (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6400 |
| <130 | 827 | 22 | 2.7 | 853 | 28 | 3.3 | 0.4530 | 1.23 | ( 0.71, 2.14) | 1.24 | ( 0.70, 2.19) | 0.01 | (-0.01, 0.02) | |
| >=130 | 1174 | 33 | 2.8 | 1199 | 35 | 2.9 | 0.8745 | 1.04 | ( 0.65, 1.66) | 1.04 | ( 0.64, 1.68) | 0.00 | (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7139 |
| <75 | 935 | 30 | 3.2 | 934 | 32 | 3.4 | 0.7929 | 1.07 | ( 0.65, 1.74) | 1.07 | ( 0.64, 1.78) | 0.00 | (-0.01, 0.02) | |
| 75 to <85 | 657 | 15 | 2.3 | 703 | 22 | 3.1 | 0.3377 | 1.37 | ( 0.72, 2.62) | 1.38 | ( 0.71, 2.69) | 0.01 | (-0.01, 0.03) | |
| >=85 | 409 | 10 | 2.4 | 415 | 9 | 2.2 | 0.7916 | 0.89 | ( 0.36, 2.16) | 0.88 | ( 0.36, 2.20) | 0.00 | (-0.02, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8132 |
| <30 | 161 | 5 | 3.1 | 148 | 7 | 4.7 | 0.4604 | 1.52 | ( 0.49, 4.69) | 1.55 | ( 0.48, 4.99) | 0.02 | (-0.03, 0.06) | |
| 30 to <45 | 550 | 21 | 3.8 | 564 | 25 | 4.4 | 0.6063 | 1.16 | ( 0.66, 2.05) | 1.17 | ( 0.65, 2.11) | 0.01 | (-0.02, 0.03) | |
| >=45 | 1289 | 29 | 2.2 | 1340 | 31 | 2.3 | 0.9130 | 1.03 | ( 0.62, 1.70) | 1.03 | ( 0.62, 1.72) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1784 |
| Normal (<30) | 764 | 24 | 3.1 | 787 | 19 | 2.4 | 0.3832 | 0.77 | ( 0.42, 1.39) | 0.76 | ( 0.41, 1.40) | -0.01 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 22 | 2.4 | 938 | 36 | 3.8 | 0.0723 | 1.61 | ( 0.95, 2.71) | 1.63 | ( 0.95, 2.79) | 0.01 | ( 0.00, 0.03) | |
| Macroalbuminuria (>300) | 311 | 8 | 2.6 | 318 | 8 | 2.5 | 0.9640 | 0.98 | ( 0.37, 2.57) | 0.98 | ( 0.36, 2.64) | 0.00 | (-0.03, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7109 |
| Low, moderate or high | 1477 | 34 | 2.3 | 1548 | 39 | 2.5 | 0.6969 | 1.09 | ( 0.69, 1.72) | 1.10 | ( 0.69, 1.75) | 0.00 | (-0.01, 0.01) | |
| Very high | 519 | 20 | 3.9 | 495 | 24 | 4.8 | 0.4370 | 1.26 | ( 0.70, 2.25) | 1.27 | ( 0.69, 2.33) | 0.01 | (-0.02, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7069 |
| No | 411 | 17 | 4.1 | 410 | 21 | 5.1 | 0.5015 | 1.24 | ( 0.66, 2.31) | 1.25 | ( 0.65, 2.41) | 0.01 | (-0.02, 0.04) | |
| Yes | 1590 | 38 | 2.4 | 1642 | 42 | 2.6 | 0.7587 | 1.07 | ( 0.69, 1.65) | 1.07 | ( 0.69, 1.67) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.0886 |
| No | 282 | 13 | 4.6 | 277 | 7 | 2.5 | 0.1850 | 0.55 | ( 0.22, 1.35) | 0.54 | ( 0.21, 1.37) | -0.02 | (-0.05, 0.01) | |
| Yes | 1719 | 42 | 2.4 | 1775 | 56 | 3.2 | 0.2028 | 1.29 | ( 0.87, 1.92) | 1.30 | ( 0.87, 1.95) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6685 |
| No | 229 | 6 | 2.6 | 250 | 9 | 3.6 | 0.5385 | 1.37 | ( 0.50, 3.80) | 1.39 | ( 0.49, 3.96) | 0.01 | (-0.02, 0.04) | |
| Yes | 1772 | 49 | 2.8 | 1802 | 54 | 3.0 | 0.6792 | 1.08 | ( 0.74, 1.59) | 1.09 | ( 0.73, 1.61) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 13 | 0.6 | 2052 | 15 | 0.7 | 0.7547 | 1.13 | ( 0.54, 2.36) | 1.13 | ( 0.53, 2.37) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.6094 |
| Male | 1065 | 9 | 0.8 | 1093 | 9 | 0.8 | 0.9559 | 0.97 | ( 0.39, 2.45) | 0.97 | ( 0.39, 2.46) | 0.00 | (-0.01, 0.01) | |
| Female | 936 | 4 | 0.4 | 959 | 6 | 0.6 | 0.5514 | 1.46 | ( 0.41, 5.17) | 1.47 | ( 0.41, 5.22) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.2535 |
| <65 | 331 | 2 | 0.6 | 313 | 0 | 0 | 0.2672 | 0.21 | ( 0.01, 4.39) | 0.21 | ( 0.01, 4.40) | -0.01 | (-0.02, 0.00) | |
| >=65 | 1670 | 11 | 0.7 | 1739 | 15 | 0.9 | 0.4940 | 1.31 | ( 0.60, 2.84) | 1.31 | ( 0.60, 2.87) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.9152 |
| North America | 273 | 2 | 0.7 | 273 | 1 | 0.4 | 0.5626 | 0.50 | ( 0.05, 5.48) | 0.50 | ( 0.04, 5.53) | 0.00 | (-0.02, 0.01) | |
| Latin America | 511 | 1 | 0.2 | 504 | 2 | 0.4 | 0.5551 | 2.03 | ( 0.18,22.29) | 2.03 | ( 0.18,22.48) | 0.00 | ( 0.00, 0.01) | |
| Europe | 865 | 7 | 0.8 | 894 | 7 | 0.8 | 0.9506 | 0.97 | ( 0.34, 2.75) | 0.97 | ( 0.34, 2.77) | 0.00 | (-0.01, 0.01) | |
| Asia | 231 | 2 | 0.9 | 248 | 3 | 1.2 | 0.7114 | 1.40 | ( 0.24, 8.29) | 1.40 | ( 0.23, 8.47) | 0.00 | (-0.01, 0.02) | |
| Other | 121 | 1 | 0.8 | 133 | 2 | 1.5 | 0.6178 | 1.82 | ( 0.17,19.81) | 1.83 | ( 0.16,20.46) | 0.01 | (-0.02, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4178 |
| Diabetic | 1045 | 8 | 0.8 | 1081 | 7 | 0.6 | 0.7452 | 0.85 | ( 0.31, 2.32) | 0.84 | ( 0.31, 2.34) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 956 | 5 | 0.5 | 971 | 8 | 0.8 | 0.4198 | 1.58 | ( 0.52, 4.80) | 1.58 | ( 0.52, 4.85) | 0.00 | ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6666 |
| <30 | 1086 | 6 | 0.6 | 1094 | 8 | 0.7 | 0.6013 | 1.32 | ( 0.46, 3.80) | 1.33 | ( 0.46, 3.83) | 0.00 | ( 0.00, 0.01) | |
| >=30 | 915 | 7 | 0.8 | 958 | 7 | 0.7 | 0.9313 | 0.96 | ( 0.34, 2.71) | 0.95 | ( 0.33, 2.73) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3984 |
| <130 | 827 | 4 | 0.5 | 853 | 7 | 0.8 | 0.3919 | 1.70 | ( 0.50, 5.77) | 1.70 | ( 0.50, 5.84) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 1174 | 9 | 0.8 | 1199 | 8 | 0.7 | 0.7741 | 0.87 | ( 0.34, 2.25) | 0.87 | ( 0.33, 2.26) | 0.00 | (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7597 |
| <75 | 935 | 7 | 0.7 | 934 | 8 | 0.9 | 0.7938 | 1.14 | ( 0.42, 3.14) | 1.15 | ( 0.41, 3.17) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 657 | 3 | 0.5 | 703 | 5 | 0.7 | 0.5395 | 1.56 | ( 0.37, 6.49) | 1.56 | ( 0.37, 6.56) | 0.00 | (-0.01, 0.01) | |
| >=85 | 409 | 3 | 0.7 | 415 | 2 | 0.5 | 0.6420 | 0.66 | ( 0.11, 3.91) | 0.66 | ( 0.11, 3.94) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6063 |
| <30 | 161 | 1 | 0.6 | 148 | 3 | 2.0 | 0.2747 | 3.26 | ( 0.34,31.03) | 3.31 | ( 0.34,32.18) | 0.01 | (-0.01, 0.04) | |
| 30 to <45 | 550 | 2 | 0.4 | 564 | 2 | 0.4 | 0.9799 | 0.98 | ( 0.14, 6.90) | 0.98 | ( 0.14, 6.95) | 0.00 | (-0.01, 0.01) | |
| >=45 | 1289 | 10 | 0.8 | 1340 | 10 | 0.7 | 0.9306 | 0.96 | ( 0.40, 2.30) | 0.96 | ( 0.40, 2.32) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2665 |
| Normal (<30) | 764 | 10 | 1.3 | 787 | 7 | 0.9 | 0.4277 | 0.68 | ( 0.26, 1.78) | 0.68 | ( 0.26, 1.79) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 2 | 0.2 | 938 | 6 | 0.6 | 0.1641 | 2.95 | ( 0.60,14.56) | 2.96 | ( 0.60,14.69) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 311 | 1 | 0.3 | 318 | 2 | 0.6 | 0.5759 | 1.96 | ( 0.18,21.46) | 1.96 | ( 0.18,21.75) | 0.00 | (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1882 |
| Low, moderate or high | 1477 | 12 | 0.8 | 1548 | 11 | 0.7 | 0.7472 | 0.87 | ( 0.39, 1.98) | 0.87 | ( 0.38, 1.99) | 0.00 | (-0.01, 0.01) | |
| Very high | 519 | 1 | 0.2 | 495 | 4 | 0.8 | 0.1620 | 4.19 | ( 0.47,37.39) | 4.22 | ( 0.47,37.89) | 0.01 | ( 0.00, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2054 |
| No | 411 | 1 | 0.2 | 410 | 4 | 1.0 | 0.1775 | 4.01 | ( 0.45,35.72) | 4.04 | ( 0.45,36.30) | 0.01 | ( 0.00, 0.02) | |
| Yes | 1590 | 12 | 0.8 | 1642 | 11 | 0.7 | 0.7743 | 0.89 | ( 0.39, 2.01) | 0.89 | ( 0.39, 2.02) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1410 |
| No | 282 | 3 | 1.1 | 277 | 0 | 0 | 0.1369 | 0.15 | (<0.01, 2.80) | 0.14 | (<0.01, 2.80) | -0.01 | (-0.02, 0.00) | |
| Yes | 1719 | 10 | 0.6 | 1775 | 15 | 0.8 | 0.3559 | 1.45 | ( 0.65, 3.22) | 1.46 | ( 0.65, 3.25) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4343 |
| No | 229 | 2 | 0.9 | 250 | 1 | 0.4 | 0.5118 | 0.46 | ( 0.04, 5.02) | 0.46 | ( 0.04, 5.06) | 0.00 | (-0.02, 0.01) | |
| Yes | 1772 | 11 | 0.6 | 1802 | 14 | 0.8 | 0.5755 | 1.25 | ( 0.57, 2.75) | 1.25 | ( 0.57, 2.77) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 52 | 2.6 | 2052 | 64 | 3.1 | 0.3207 | 1.20 | ( 0.84, 1.72) | 1.21 | ( 0.83, 1.75) | 0.01 | (-0.01, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.8068 |
| Male | 1065 | 32 | 3.0 | 1093 | 38 | 3.5 | 0.5361 | 1.16 | ( 0.73, 1.84) | 1.16 | ( 0.72, 1.88) | 0.00 | (-0.01, 0.02) | |
| Female | 936 | 20 | 2.1 | 959 | 26 | 2.7 | 0.4166 | 1.27 | ( 0.71, 2.26) | 1.28 | ( 0.71, 2.30) | 0.01 | (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.5926 |
| <65 | 331 | 5 | 1.5 | 313 | 4 | 1.3 | 0.8015 | 0.85 | ( 0.23, 3.12) | 0.84 | ( 0.22, 3.17) | 0.00 | (-0.02, 0.02) | |
| >=65 | 1670 | 47 | 2.8 | 1739 | 60 | 3.5 | 0.2871 | 1.23 | ( 0.84, 1.79) | 1.23 | ( 0.84, 1.82) | 0.01 | (-0.01, 0.02) | |
| Region | | | | | | | | | | | | | | 0.2219 |
| North America | 273 | 17 | 6.2 | 273 | 23 | 8.4 | 0.3244 | 1.35 | ( 0.74, 2.48) | 1.39 | ( 0.72, 2.66) | 0.02 | (-0.02, 0.07) | |
| Latin America | 511 | 5 | 1.0 | 504 | 15 | 3.0 | 0.0220 | 3.04 | ( 1.11, 8.31) | 3.10 | ( 1.12, 8.61) | 0.02 | ( 0.00, 0.04) | |
| Europe | 865 | 21 | 2.4 | 894 | 19 | 2.1 | 0.6705 | 0.88 | ( 0.47, 1.62) | 0.87 | ( 0.47, 1.63) | 0.00 | (-0.02, 0.01) | |
| Asia | 231 | 3 | 1.3 | 248 | 3 | 1.2 | 0.9302 | 0.93 | ( 0.19, 4.57) | 0.93 | ( 0.19, 4.66) | 0.00 | (-0.02, 0.02) | |
| Other | 121 | 6 | 5.0 | 133 | 4 | 3.0 | 0.4245 | 0.61 | ( 0.18, 2.10) | 0.59 | ( 0.16, 2.16) | -0.02 | (-0.07, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4479 |
| Diabetic | 1045 | 31 | 3.0 | 1081 | 34 | 3.1 | 0.8109 | 1.06 | ( 0.66, 1.71) | 1.06 | ( 0.65, 1.74) | 0.00 | (-0.01, 0.02) | |
| Non-Diabetic | 956 | 21 | 2.2 | 971 | 30 | 3.1 | 0.2221 | 1.41 | ( 0.81, 2.44) | 1.42 | ( 0.81, 2.50) | 0.01 | (-0.01, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2672 |
| <30 | 1086 | 22 | 2.0 | 1094 | 33 | 3.0 | 0.1403 | 1.49 | ( 0.87, 2.54) | 1.50 | ( 0.87, 2.60) | 0.01 | ( 0.00, 0.02) | |
| >=30 | 915 | 30 | 3.3 | 958 | 31 | 3.2 | 0.9584 | 0.99 | ( 0.60, 1.62) | 0.99 | ( 0.59, 1.64) | 0.00 | (-0.02, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8320 |
| <130 | 827 | 22 | 2.7 | 853 | 26 | 3.0 | 0.6333 | 1.15 | ( 0.65, 2.01) | 1.15 | ( 0.65, 2.05) | 0.00 | (-0.01, 0.02) | |
| >=130 | 1174 | 30 | 2.6 | 1199 | 38 | 3.2 | 0.3701 | 1.24 | ( 0.77, 1.99) | 1.25 | ( 0.77, 2.03) | 0.01 | (-0.01, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9200 |
| <75 | 935 | 28 | 3.0 | 934 | 35 | 3.7 | 0.3673 | 1.25 | ( 0.77, 2.04) | 1.26 | ( 0.76, 2.09) | 0.01 | (-0.01, 0.02) | |
| 75 to <85 | 657 | 17 | 2.6 | 703 | 22 | 3.1 | 0.5496 | 1.21 | ( 0.65, 2.26) | 1.22 | ( 0.64, 2.31) | 0.01 | (-0.01, 0.02) | |
| >=85 | 409 | 7 | 1.7 | 415 | 7 | 1.7 | 0.9781 | 0.99 | ( 0.35, 2.78) | 0.99 | ( 0.34, 2.83) | 0.00 | (-0.02, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1856 |
| <30 | 161 | 4 | 2.5 | 148 | 10 | 6.8 | 0.0712 | 2.72 | ( 0.87, 8.49) | 2.84 | ( 0.87, 9.27) | 0.04 | ( 0.00, 0.09) | |
| 30 to <45 | 550 | 21 | 3.8 | 564 | 18 | 3.2 | 0.5694 | 0.84 | ( 0.45, 1.55) | 0.83 | ( 0.44, 1.58) | -0.01 | (-0.03, 0.02) | |
| >=45 | 1289 | 27 | 2.1 | 1340 | 36 | 2.7 | 0.3212 | 1.28 | ( 0.78, 2.10) | 1.29 | ( 0.78, 2.14) | 0.01 | (-0.01, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6571 |
| Normal (<30) | 764 | 20 | 2.6 | 787 | 21 | 2.7 | 0.9505 | 1.02 | ( 0.56, 1.87) | 1.02 | ( 0.55, 1.90) | 0.00 | (-0.02, 0.02) | |
| Microalbuminuria (30 to <=300) | 921 | 25 | 2.7 | 938 | 36 | 3.8 | 0.1740 | 1.41 | ( 0.86, 2.34) | 1.43 | ( 0.85, 2.40) | 0.01 | ( 0.00, 0.03) | |
| Macroalbuminuria (>300) | 311 | 7 | 2.3 | 318 | 7 | 2.2 | 0.9664 | 0.98 | ( 0.35, 2.76) | 0.98 | ( 0.34, 2.82) | 0.00 | (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1743 |
| Low, moderate or high | 1477 | 36 | 2.4 | 1548 | 38 | 2.5 | 0.9753 | 1.01 | ( 0.64, 1.58) | 1.01 | ( 0.63, 1.60) | 0.00 | (-0.01, 0.01) | |
| Very high | 519 | 16 | 3.1 | 495 | 26 | 5.3 | 0.0831 | 1.70 | ( 0.93, 3.14) | 1.74 | ( 0.92, 3.29) | 0.02 | ( 0.00, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9985 |
| No | 411 | 15 | 3.6 | 410 | 18 | 4.4 | 0.5891 | 1.20 | ( 0.61, 2.35) | 1.21 | ( 0.60, 2.44) | 0.01 | (-0.02, 0.03) | |
| Yes | 1590 | 37 | 2.3 | 1642 | 46 | 2.8 | 0.3940 | 1.20 | ( 0.79, 1.85) | 1.21 | ( 0.78, 1.88) | 0.00 | (-0.01, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8930 |
| No | 282 | 8 | 2.8 | 277 | 10 | 3.6 | 0.6046 | 1.27 | ( 0.51, 3.18) | 1.28 | ( 0.50, 3.30) | 0.01 | (-0.02, 0.04) | |
| Yes | 1719 | 44 | 2.6 | 1775 | 54 | 3.0 | 0.3877 | 1.19 | ( 0.80, 1.76) | 1.19 | ( 0.80, 1.79) | 0.00 | (-0.01, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6257 |
| No | 229 | 4 | 1.7 | 250 | 7 | 2.8 | 0.4420 | 1.60 | ( 0.48, 5.40) | 1.62 | ( 0.47, 5.61) | 0.01 | (-0.02, 0.04) | |
| Yes | 1772 | 48 | 2.7 | 1802 | 57 | 3.2 | 0.4213 | 1.17 | ( 0.80, 1.70) | 1.17 | ( 0.79, 1.73) | 0.00 | (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 43 | 2.1 | 2052 | 57 | 2.8 | 0.1970 | 1.29 | ( 0.87, 1.91) | 1.30 | ( 0.87, 1.94) | 0.01 | ( 0.00, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.6477 |
| Male | 1065 | 26 | 2.4 | 1093 | 37 | 3.4 | 0.1929 | 1.39 | ( 0.85, 2.27) | 1.40 | ( 0.84, 2.33) | 0.01 | ( 0.00, 0.02) | |
| Female | 936 | 17 | 1.8 | 959 | 20 | 2.1 | 0.6719 | 1.15 | ( 0.61, 2.18) | 1.15 | ( 0.60, 2.21) | 0.00 | (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.5106 |
| <65 | 331 | 5 | 1.5 | 313 | 4 | 1.3 | 0.8015 | 0.85 | ( 0.23, 3.12) | 0.84 | ( 0.22, 3.17) | 0.00 | (-0.02, 0.02) | |
| >=65 | 1670 | 38 | 2.3 | 1739 | 53 | 3.0 | 0.1620 | 1.34 | ( 0.89, 2.02) | 1.35 | ( 0.89, 2.06) | 0.01 | ( 0.00, 0.02) | |
| Region | | | | | | | | | | | | | | 0.4892 |
| North America | 273 | 16 | 5.9 | 273 | 21 | 7.7 | 0.3946 | 1.31 | ( 0.70, 2.46) | 1.34 | ( 0.68, 2.62) | 0.02 | (-0.02, 0.06) | |
| Latin America | 511 | 4 | 0.8 | 504 | 12 | 2.4 | 0.0410 | 3.04 | ( 0.99, 9.37) | 3.09 | ( 0.99, 9.65) | 0.02 | ( 0.00, 0.03) | |
| Europe | 865 | 16 | 1.8 | 894 | 17 | 1.9 | 0.9361 | 1.03 | ( 0.52, 2.02) | 1.03 | ( 0.52, 2.05) | 0.00 | (-0.01, 0.01) | |
| Asia | 231 | 2 | 0.9 | 248 | 3 | 1.2 | 0.7114 | 1.40 | ( 0.24, 8.29) | 1.40 | ( 0.23, 8.47) | 0.00 | (-0.01, 0.02) | |
| Other | 121 | 5 | 4.1 | 133 | 4 | 3.0 | 0.6282 | 0.73 | ( 0.20, 2.65) | 0.72 | ( 0.19, 2.74) | -0.01 | (-0.06, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8498 |
| Diabetic | 1045 | 24 | 2.3 | 1081 | 31 | 2.9 | 0.4070 | 1.25 | ( 0.74, 2.11) | 1.26 | ( 0.73, 2.15) | 0.01 | (-0.01, 0.02) | |
| Non-Diabetic | 956 | 19 | 2.0 | 971 | 26 | 2.7 | 0.3158 | 1.35 | ( 0.75, 2.42) | 1.36 | ( 0.75, 2.47) | 0.01 | (-0.01, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5540 |
| <30 | 1086 | 19 | 1.7 | 1094 | 28 | 2.6 | 0.1930 | 1.46 | ( 0.82, 2.60) | 1.48 | ( 0.82, 2.66) | 0.01 | ( 0.00, 0.02) | |
| >=30 | 915 | 24 | 2.6 | 958 | 29 | 3.0 | 0.5980 | 1.15 | ( 0.68, 1.97) | 1.16 | ( 0.67, 2.01) | 0.00 | (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9997 |
| <130 | 827 | 18 | 2.2 | 853 | 24 | 2.8 | 0.4031 | 1.29 | ( 0.71, 2.36) | 1.30 | ( 0.70, 2.42) | 0.01 | (-0.01, 0.02) | |
| >=130 | 1174 | 25 | 2.1 | 1199 | 33 | 2.8 | 0.3259 | 1.29 | ( 0.77, 2.16) | 1.30 | ( 0.77, 2.20) | 0.01 | (-0.01, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8170 |
| <75 | 935 | 22 | 2.4 | 934 | 32 | 3.4 | 0.1661 | 1.46 | ( 0.85, 2.49) | 1.47 | ( 0.85, 2.55) | 0.01 | ( 0.00, 0.03) | |
| 75 to <85 | 657 | 15 | 2.3 | 703 | 18 | 2.6 | 0.7398 | 1.12 | ( 0.57, 2.21) | 1.12 | ( 0.56, 2.25) | 0.00 | (-0.01, 0.02) | |
| >=85 | 409 | 6 | 1.5 | 415 | 7 | 1.7 | 0.8002 | 1.15 | ( 0.39, 3.39) | 1.15 | ( 0.38, 3.46) | 0.00 | (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2835 |
| <30 | 161 | 3 | 1.9 | 148 | 8 | 5.4 | 0.0932 | 2.90 | ( 0.78,10.73) | 3.01 | ( 0.78,11.57) | 0.04 | (-0.01, 0.08) | |
| 30 to <45 | 550 | 17 | 3.1 | 564 | 16 | 2.8 | 0.8026 | 0.92 | ( 0.47, 1.80) | 0.92 | ( 0.46, 1.83) | 0.00 | (-0.02, 0.02) | |
| >=45 | 1289 | 23 | 1.8 | 1340 | 33 | 2.5 | 0.2285 | 1.38 | ( 0.81, 2.34) | 1.39 | ( 0.81, 2.38) | 0.01 | ( 0.00, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9783 |
| Normal (<30) | 764 | 16 | 2.1 | 787 | 21 | 2.7 | 0.4588 | 1.27 | ( 0.67, 2.42) | 1.28 | ( 0.66, 2.48) | 0.01 | (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 921 | 22 | 2.4 | 938 | 30 | 3.2 | 0.2899 | 1.34 | ( 0.78, 2.30) | 1.35 | ( 0.77, 2.36) | 0.01 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 311 | 5 | 1.6 | 318 | 6 | 1.9 | 0.7895 | 1.17 | ( 0.36, 3.81) | 1.18 | ( 0.36, 3.90) | 0.00 | (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2705 |
| Low, moderate or high | 1477 | 30 | 2.0 | 1548 | 35 | 2.3 | 0.6630 | 1.11 | ( 0.69, 1.80) | 1.12 | ( 0.68, 1.83) | 0.00 | (-0.01, 0.01) | |
| Very high | 519 | 13 | 2.5 | 495 | 22 | 4.4 | 0.0908 | 1.77 | ( 0.90, 3.48) | 1.81 | ( 0.90, 3.63) | 0.02 | ( 0.00, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6065 |
| No | 411 | 12 | 2.9 | 410 | 13 | 3.2 | 0.8342 | 1.09 | ( 0.50, 2.35) | 1.09 | ( 0.49, 2.42) | 0.00 | (-0.02, 0.03) | |
| Yes | 1590 | 31 | 1.9 | 1642 | 44 | 2.7 | 0.1682 | 1.37 | ( 0.87, 2.16) | 1.38 | ( 0.87, 2.20) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7926 |
| No | 282 | 7 | 2.5 | 277 | 10 | 3.6 | 0.4375 | 1.45 | ( 0.56, 3.77) | 1.47 | ( 0.55, 3.92) | 0.01 | (-0.02, 0.04) | |
| Yes | 1719 | 36 | 2.1 | 1775 | 47 | 2.6 | 0.2827 | 1.26 | ( 0.82, 1.94) | 1.27 | ( 0.82, 1.97) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6042 |
| No | 229 | 3 | 1.3 | 250 | 6 | 2.4 | 0.3802 | 1.83 | ( 0.46, 7.24) | 1.85 | ( 0.46, 7.49) | 0.01 | (-0.01, 0.03) | |
| Yes | 1772 | 40 | 2.3 | 1802 | 51 | 2.8 | 0.2770 | 1.25 | ( 0.83, 1.89) | 1.26 | ( 0.83, 1.92) | 0.01 | ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 173 | 8.6 | 2052 | 140 | 6.8 | 0.0297 | 0.79 | ( 0.64, 0.98) | 0.77 | ( 0.61, 0.98) | -0.02 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.2835 |
| Male | 1065 | 99 | 9.3 | 1093 | 72 | 6.6 | 0.0199 | 0.71 | ( 0.53, 0.95) | 0.69 | ( 0.50, 0.94) | -0.03 | (-0.05, 0.00) | |
| Female | 936 | 74 | 7.9 | 959 | 68 | 7.1 | 0.5004 | 0.90 | ( 0.65, 1.23) | 0.89 | ( 0.63, 1.25) | -0.01 | (-0.03, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.9482 |
| <65 | 331 | 29 | 8.8 | 313 | 22 | 7.0 | 0.4158 | 0.80 | ( 0.47, 1.37) | 0.79 | ( 0.44, 1.40) | -0.02 | (-0.06, 0.02) | |
| >=65 | 1670 | 144 | 8.6 | 1739 | 118 | 6.8 | 0.0441 | 0.79 | ( 0.62, 0.99) | 0.77 | ( 0.60, 0.99) | -0.02 | (-0.04, 0.00) | |
| Region | | | | | | | | | | | | | | 0.4058 |
| North America | 273 | 52 | 19.0 | 273 | 43 | 15.8 | 0.3096 | 0.83 | ( 0.57, 1.19) | 0.79 | ( 0.51, 1.24) | -0.03 | (-0.10, 0.03) | |
| Latin America | 511 | 37 | 7.2 | 504 | 38 | 7.5 | 0.8555 | 1.04 | ( 0.67, 1.61) | 1.04 | ( 0.65, 1.67) | 0.00 | (-0.03, 0.04) | |
| Europe | 865 | 58 | 6.7 | 894 | 36 | 4.0 | 0.0125 | 0.60 | ( 0.40, 0.90) | 0.58 | ( 0.38, 0.89) | -0.03 | (-0.05,-0.01) | |
| Asia | 231 | 12 | 5.2 | 248 | 8 | 3.2 | 0.2817 | 0.62 | ( 0.26, 1.49) | 0.61 | ( 0.24, 1.52) | -0.02 | (-0.06, 0.02) | |
| Other | 121 | 14 | 11.6 | 133 | 15 | 11.3 | 0.9417 | 0.97 | ( 0.49, 1.93) | 0.97 | ( 0.45, 2.11) | 0.00 | (-0.08, 0.08) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8497 |
| Diabetic | 1045 | 110 | 10.5 | 1081 | 91 | 8.4 | 0.0967 | 0.80 | ( 0.61, 1.04) | 0.78 | ( 0.58, 1.05) | -0.02 | (-0.05, 0.00) | |
| Non-Diabetic | 956 | 63 | 6.6 | 971 | 49 | 5.0 | 0.1476 | 0.77 | ( 0.53, 1.10) | 0.75 | ( 0.51, 1.11) | -0.02 | (-0.04, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1023 |
| <30 | 1086 | 85 | 7.8 | 1094 | 55 | 5.0 | 0.0077 | 0.64 | ( 0.46, 0.89) | 0.62 | ( 0.44, 0.88) | -0.03 | (-0.05,-0.01) | |
| >=30 | 915 | 88 | 9.6 | 958 | 85 | 8.9 | 0.5779 | 0.92 | ( 0.69, 1.23) | 0.92 | ( 0.67, 1.25) | -0.01 | (-0.03, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1950 |
| <130 | 827 | 69 | 8.3 | 853 | 66 | 7.7 | 0.6478 | 0.93 | ( 0.67, 1.28) | 0.92 | ( 0.65, 1.31) | -0.01 | (-0.03, 0.02) | |
| >=130 | 1174 | 104 | 8.9 | 1199 | 74 | 6.2 | 0.0130 | 0.70 | ( 0.52, 0.93) | 0.68 | ( 0.50, 0.92) | -0.03 | (-0.05,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8146 |
| <75 | 935 | 95 | 10.2 | 934 | 80 | 8.6 | 0.2366 | 0.84 | ( 0.64, 1.12) | 0.83 | ( 0.61, 1.13) | -0.02 | (-0.04, 0.01) | |
| 75 to <85 | 657 | 49 | 7.5 | 703 | 38 | 5.4 | 0.1221 | 0.72 | ( 0.48, 1.09) | 0.71 | ( 0.46, 1.10) | -0.02 | (-0.05, 0.01) | |
| >=85 | 409 | 29 | 7.1 | 415 | 22 | 5.3 | 0.2865 | 0.75 | ( 0.44, 1.28) | 0.73 | ( 0.41, 1.30) | -0.02 | (-0.05, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9274 |
| <30 | 161 | 36 | 22.4 | 148 | 28 | 18.9 | 0.4558 | 0.85 | ( 0.54, 1.31) | 0.81 | ( 0.47, 1.41) | -0.03 | (-0.12, 0.06) | |
| 30 to <45 | 550 | 58 | 10.5 | 564 | 49 | 8.7 | 0.2928 | 0.82 | ( 0.57, 1.18) | 0.81 | ( 0.54, 1.20) | -0.02 | (-0.05, 0.02) | |
| >=45 | 1289 | 79 | 6.1 | 1340 | 63 | 4.7 | 0.1056 | 0.77 | ( 0.56, 1.06) | 0.76 | ( 0.54, 1.06) | -0.01 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7851 |
| Normal (<30) | 764 | 52 | 6.8 | 787 | 41 | 5.2 | 0.1855 | 0.77 | ( 0.51, 1.14) | 0.75 | ( 0.49, 1.15) | -0.02 | (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 82 | 8.9 | 938 | 63 | 6.7 | 0.0787 | 0.75 | ( 0.55, 1.03) | 0.74 | ( 0.52, 1.04) | -0.02 | (-0.05, 0.00) | |
| Macroalbuminuria (>300) | 311 | 39 | 12.5 | 318 | 36 | 11.3 | 0.6370 | 0.90 | ( 0.59, 1.38) | 0.89 | ( 0.55, 1.44) | -0.01 | (-0.06, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5630 |
| Low, moderate or high | 1477 | 94 | 6.4 | 1548 | 75 | 4.8 | 0.0690 | 0.76 | ( 0.57, 1.02) | 0.75 | ( 0.55, 1.02) | -0.02 | (-0.03, 0.00) | |
| Very high | 519 | 79 | 15.2 | 495 | 65 | 13.1 | 0.3405 | 0.86 | ( 0.64, 1.17) | 0.84 | ( 0.59, 1.20) | -0.02 | (-0.06, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7420 |
| No | 411 | 38 | 9.2 | 410 | 32 | 7.8 | 0.4598 | 0.84 | ( 0.54, 1.32) | 0.83 | ( 0.51, 1.36) | -0.01 | (-0.05, 0.02) | |
| Yes | 1590 | 135 | 8.5 | 1642 | 108 | 6.6 | 0.0392 | 0.77 | ( 0.61, 0.99) | 0.76 | ( 0.58, 0.99) | -0.02 | (-0.04, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1971 |
| No | 282 | 28 | 9.9 | 277 | 15 | 5.4 | 0.0452 | 0.55 | ( 0.30,<1.00) | 0.52 | ( 0.27, 1.00) | -0.05 | (-0.09, 0.00) | |
| Yes | 1719 | 145 | 8.4 | 1775 | 125 | 7.0 | 0.1232 | 0.83 | ( 0.66, 1.05) | 0.82 | ( 0.64, 1.05) | -0.01 | (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.0916 |
| No | 229 | 15 | 6.6 | 250 | 6 | 2.4 | 0.0267 | 0.37 | ( 0.14, 0.93) | 0.35 | ( 0.13, 0.92) | -0.04 | (-0.08, 0.00) | |
| Yes | 1772 | 158 | 8.9 | 1802 | 134 | 7.4 | 0.1062 | 0.83 | ( 0.67, 1.04) | 0.82 | ( 0.65, 1.04) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 6 | 0.3 | 2052 | 5 | 0.2 | 0.7310 | 0.81 | ( 0.25, 2.66) | 0.81 | ( 0.25, 2.67) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | |
| Male | 1065 | 2 | 0.2 | 1093 | 4 | 0.4 | | | | | | | | |
| Female | 936 | 4 | 0.4 | 959 | 1 | 0.1 | | | | | | | | |
| Age [years] | | | | | | | | | | | | | | 0.3615 |
| <65 | 331 | 0 | 0 | 313 | 1 | 0.3 | 0.4545 | 3.17 | ( 0.13,77.57) | 3.18 | ( 0.13,78.41) | 0.00 | (-0.01, 0.01) | |
| >=65 | 1670 | 6 | 0.4 | 1739 | 4 | 0.2 | 0.4854 | 0.64 | ( 0.18, 2.26) | 0.64 | ( 0.18, 2.27) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | |
| North America | 273 | 3 | 1.1 | 273 | 3 | 1.1 | | | | | | | | |
| Latin America | 511 | 0 | 0 | 504 | 0 | 0 | | | | | | | | |
| Europe | 865 | 2 | 0.2 | 894 | 0 | 0 | | | | | | | | |
| Asia | 231 | 1 | 0.4 | 248 | 1 | 0.4 | | | | | | | | |
| Other | 121 | 0 | 0 | 133 | 1 | 0.8 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | |
| Diabetic | 1045 | 3 | 0.3 | 1081 | 1 | 0.1 | | | | | | | | |
| Non-Diabetic | 956 | 3 | 0.3 | 971 | 4 | 0.4 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | |
| <30 | 1086 | 4 | 0.4 | 1094 | 3 | 0.3 | | | | | | | | |
| >=30 | 915 | 2 | 0.2 | 958 | 2 | 0.2 | | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | |
| <130 | 827 | 2 | 0.2 | 853 | 2 | 0.2 | | | | | | | | |
| >=130 | 1174 | 4 | 0.3 | 1199 | 3 | 0.3 | | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | |
| <75 | 935 | 4 | 0.4 | 934 | 3 | 0.3 | | | | | | | | |
| 75 to <85 | 657 | 2 | 0.3 | 703 | 0 | 0 | | | | | | | | |
| >=85 | 409 | 0 | 0 | 415 | 2 | 0.5 | | | | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 161 | 1 | 0.6 | 148 | 1 | 0.7 | | | | | |
| 30 to <45 | 550 | 2 | 0.4 | 564 | 1 | 0.2 | | | | | |
| >=45 | 1289 | 3 | 0.2 | 1340 | 3 | 0.2 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 764 | 3 | 0.4 | 787 | 2 | 0.3 | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 3 | 0.3 | 938 | 1 | 0.1 | | | | | |
| Macroalbuminuria (>300) | 311 | 0 | 0 | 318 | 2 | 0.6 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1477 | 5 | 0.3 | 1548 | 3 | 0.2 | | | | | |
| Very high | 519 | 1 | 0.2 | 495 | 2 | 0.4 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 411 | 2 | 0.5 | 410 | 1 | 0.2 | | | | | |
| Yes | 1590 | 4 | 0.3 | 1642 | 4 | 0.2 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 282 | 1 | 0.4 | 277 | 1 | 0.4 | | | | | |
| Yes | 1719 | 5 | 0.3 | 1775 | 4 | 0.2 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | 0.9573 |
| No | 229 | 0 | 0 | 250 | 0 | 0 | 0.9651 | 0.92 ( 0.02,45.99) | 0.92 ( 0.02,46.36) | 0.00 (-0.01, 0.01) | |
| Yes | 1772 | 6 | 0.3 | 1802 | 5 | 0.3 | 0.7415 | 0.82 ( 0.25, 2.68) | 0.82 ( 0.25, 2.69) | 0.00 ( 0.00, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 9 | 0.4 | 2052 | 7 | 0.3 | 0.5813 | 0.76 | ( 0.28, 2.03) | 0.76 | ( 0.28, 2.04) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.6951 |
| Male | 1065 | 6 | 0.6 | 1093 | 4 | 0.4 | 0.4996 | 0.65 | ( 0.18, 2.30) | 0.65 | ( 0.18, 2.30) | 0.00 | (-0.01, 0.00) | |
| Female | 936 | 3 | 0.3 | 959 | 3 | 0.3 | 0.9762 | 0.98 | ( 0.20, 4.82) | 0.98 | ( 0.20, 4.85) | 0.00 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.3502 |
| <65 | 331 | 1 | 0.3 | 313 | 2 | 0.6 | 0.5304 | 2.12 | ( 0.19,23.21) | 2.12 | ( 0.19,23.52) | 0.00 | (-0.01, 0.01) | |
| >=65 | 1670 | 8 | 0.5 | 1739 | 5 | 0.3 | 0.3644 | 0.60 | ( 0.20, 1.83) | 0.60 | ( 0.20, 1.83) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | |
| North America | 273 | 1 | 0.4 | 273 | 3 | 1.1 | | | | | | | | |
| Latin America | 511 | 3 | 0.6 | 504 | 0 | 0 | | | | | | | | |
| Europe | 865 | 4 | 0.5 | 894 | 1 | 0.1 | | | | | | | | |
| Asia | 231 | 0 | 0 | 248 | 1 | 0.4 | | | | | | | | |
| Other | 121 | 1 | 0.8 | 133 | 2 | 1.5 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8959 |
| Diabetic | 1045 | 9 | 0.9 | 1081 | 7 | 0.6 | 0.5687 | 0.75 | ( 0.28, 2.01) | 0.75 | ( 0.28, 2.02) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 956 | 0 | 0 | 971 | 0 | 0 | 0.9938 | 0.98 | ( 0.02,49.57) | 0.98 | ( 0.02,49.67) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7458 |
| <30 | 1086 | 2 | 0.2 | 1094 | 2 | 0.2 | 0.9941 | 0.99 | ( 0.14, 7.03) | 0.99 | ( 0.14, 7.06) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 915 | 7 | 0.8 | 958 | 5 | 0.5 | 0.5098 | 0.68 | ( 0.22, 2.14) | 0.68 | ( 0.22, 2.15) | 0.00 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | |
| <130 | 827 | 5 | 0.6 | 853 | 3 | 0.4 | | | | | | | | |
| >=130 | 1174 | 4 | 0.3 | 1199 | 4 | 0.3 | | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | |
| <75 | 935 | 5 | 0.5 | 934 | 2 | 0.2 | | | | | | | | |
| 75 to <85 | 657 | 4 | 0.6 | 703 | 5 | 0.7 | | | | | | | | |
| >=85 | 409 | 0 | 0 | 415 | 0 | 0 | | | | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 161 | 1 | 0.6 | 148 | 2 | 1.4 | | | | | |
| 30 to <45 | 550 | 1 | 0.2 | 564 | 3 | 0.5 | | | | | |
| >=45 | 1289 | 7 | 0.5 | 1340 | 2 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 764 | 3 | 0.4 | 787 | 1 | 0.1 | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 4 | 0.4 | 938 | 5 | 0.5 | | | | | |
| Macroalbuminuria (>300) | 311 | 2 | 0.6 | 318 | 1 | 0.3 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1477 | 5 | 0.3 | 1548 | 3 | 0.2 | | | | | |
| Very high | 519 | 4 | 0.8 | 495 | 4 | 0.8 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3654 |
| No | 411 | 2 | 0.5 | 410 | 3 | 0.7 | 0.6518 | 1.50 ( 0.25, 8.95) | 1.51 ( 0.25, 9.07) | 0.00 (-0.01, 0.01) | |
| Yes | 1590 | 7 | 0.4 | 1642 | 4 | 0.2 | 0.3372 | 0.55 ( 0.16, 1.89) | 0.55 ( 0.16, 1.89) | 0.00 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.8232 |
| No | 282 | 1 | 0.4 | 277 | 1 | 0.4 | 0.9899 | 1.02 ( 0.06,16.20) | 1.02 ( 0.06,16.36) | 0.00 (-0.01, 0.01) | |
| Yes | 1719 | 8 | 0.5 | 1775 | 6 | 0.3 | 0.5513 | 0.73 ( 0.25, 2.09) | 0.73 ( 0.25, 2.10) | 0.00 (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.8859 |
| No | 229 | 1 | 0.4 | 250 | 1 | 0.4 | 0.9504 | 0.92 ( 0.06,14.56) | 0.92 ( 0.06,14.72) | 0.00 (-0.01, 0.01) | |
| Yes | 1772 | 8 | 0.5 | 1802 | 6 | 0.3 | 0.5707 | 0.74 ( 0.26, 2.12) | 0.74 ( 0.26, 2.13) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 20 | 1.0 | 2052 | 13 | 0.6 | 0.1949 | 0.63 | ( 0.32, 1.27) | 0.63 | ( 0.31, 1.27) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.8023 |
| Male | 1065 | 13 | 1.2 | 1093 | 9 | 0.8 | 0.3584 | 0.67 | ( 0.29, 1.57) | 0.67 | ( 0.29, 1.58) | 0.00 | (-0.01, 0.00) | |
| Female | 936 | 7 | 0.7 | 959 | 4 | 0.4 | 0.3433 | 0.56 | ( 0.16, 1.90) | 0.56 | ( 0.16, 1.91) | 0.00 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.2656 |
| <65 | 331 | 5 | 1.5 | 313 | 1 | 0.3 | 0.1158 | 0.21 | ( 0.02, 1.80) | 0.21 | ( 0.02, 1.80) | -0.01 | (-0.03, 0.00) | |
| >=65 | 1670 | 15 | 0.9 | 1739 | 12 | 0.7 | 0.4931 | 0.77 | ( 0.36, 1.64) | 0.77 | ( 0.36, 1.64) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.6851 |
| North America | 273 | 4 | 1.5 | 273 | 4 | 1.5 | 1.0000 | 1.00 | ( 0.25, 3.96) | 1.00 | ( 0.25, 4.04) | 0.00 | (-0.02, 0.02) | |
| Latin America | 511 | 7 | 1.4 | 504 | 4 | 0.8 | 0.3753 | 0.58 | ( 0.17, 1.97) | 0.58 | ( 0.17, 1.98) | -0.01 | (-0.02, 0.01) | |
| Europe | 865 | 4 | 0.5 | 894 | 1 | 0.1 | 0.1674 | 0.24 | ( 0.03, 2.16) | 0.24 | ( 0.03, 2.16) | 0.00 | (-0.01, 0.00) | |
| Asia | 231 | 3 | 1.3 | 248 | 1 | 0.4 | 0.2819 | 0.31 | ( 0.03, 2.96) | 0.31 | ( 0.03, 2.98) | -0.01 | (-0.03, 0.01) | |
| Other | 121 | 2 | 1.7 | 133 | 3 | 2.3 | 0.7298 | 1.36 | ( 0.23, 8.03) | 1.37 | ( 0.23, 8.36) | 0.01 | (-0.03, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4819 |
| Diabetic | 1045 | 13 | 1.2 | 1081 | 10 | 0.9 | 0.4773 | 0.74 | ( 0.33, 1.69) | 0.74 | ( 0.32, 1.70) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 956 | 7 | 0.7 | 971 | 3 | 0.3 | 0.1960 | 0.42 | ( 0.11, 1.63) | 0.42 | ( 0.11, 1.63) | 0.00 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2090 |
| <30 | 1086 | 8 | 0.7 | 1094 | 8 | 0.7 | 0.9882 | 0.99 | ( 0.37, 2.64) | 0.99 | ( 0.37, 2.65) | 0.00 | (-0.01, 0.01) | |
| >=30 | 915 | 12 | 1.3 | 958 | 5 | 0.5 | 0.0717 | 0.40 | ( 0.14, 1.13) | 0.39 | ( 0.14, 1.13) | -0.01 | (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1029 |
| <130 | 827 | 12 | 1.5 | 853 | 4 | 0.5 | 0.0383 | 0.32 | ( 0.10,<1.00) | 0.32 | ( 0.10, 1.00) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1174 | 8 | 0.7 | 1199 | 9 | 0.8 | 0.8416 | 1.10 | ( 0.43, 2.85) | 1.10 | ( 0.42, 2.87) | 0.00 | (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6006 |
| <75 | 935 | 9 | 1.0 | 934 | 8 | 0.9 | 0.8092 | 0.89 | ( 0.34, 2.30) | 0.89 | ( 0.34, 2.31) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 657 | 7 | 1.1 | 703 | 3 | 0.4 | 0.1683 | 0.40 | ( 0.10, 1.54) | 0.40 | ( 0.10, 1.55) | -0.01 | (-0.02, 0.00) | |
| >=85 | 409 | 4 | 1.0 | 415 | 2 | 0.5 | 0.4024 | 0.49 | ( 0.09, 2.68) | 0.49 | ( 0.09, 2.69) | 0.00 | (-0.02, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.9357 |
| <30 | 161 | 4 | 2.5 | 148 | 3 | 2.0 | 0.7872 | 0.82 ( 0.19, 3.58) | 0.81 ( 0.18, 3.69) | 0.00 (-0.04, 0.03) | |
| 30 to <45 | 550 | 10 | 1.8 | 564 | 6 | 1.1 | 0.2901 | 0.59 ( 0.21, 1.60) | 0.58 ( 0.21, 1.61) | -0.01 (-0.02, 0.01) | |
| >=45 | 1289 | 6 | 0.5 | 1340 | 4 | 0.3 | 0.4869 | 0.64 ( 0.18, 2.27) | 0.64 ( 0.18, 2.27) | 0.00 (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.7084 |
| Normal (<30) | 764 | 9 | 1.2 | 787 | 4 | 0.5 | 0.1481 | 0.43 ( 0.13, 1.40) | 0.43 ( 0.13, 1.40) | -0.01 (-0.02, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 5 | 0.5 | 938 | 4 | 0.4 | 0.7176 | 0.79 ( 0.21, 2.92) | 0.78 ( 0.21, 2.93) | 0.00 (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 311 | 6 | 1.9 | 318 | 5 | 1.6 | 0.7328 | 0.81 ( 0.25, 2.64) | 0.81 ( 0.25, 2.69) | 0.00 (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.2896 |
| Low, moderate or high | 1477 | 11 | 0.7 | 1548 | 5 | 0.3 | 0.1099 | 0.43 ( 0.15, 1.25) | 0.43 ( 0.15, 1.25) | 0.00 (-0.01, 0.00) | |
| Very high | 519 | 9 | 1.7 | 495 | 8 | 1.6 | 0.8837 | 0.93 ( 0.36, 2.40) | 0.93 ( 0.36, 2.43) | 0.00 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.9480 |
| No | 411 | 3 | 0.7 | 410 | 2 | 0.5 | 0.6557 | 0.67 ( 0.11, 3.98) | 0.67 ( 0.11, 4.01) | 0.00 (-0.01, 0.01) | |
| Yes | 1590 | 17 | 1.1 | 1642 | 11 | 0.7 | 0.2208 | 0.63 ( 0.29, 1.33) | 0.62 ( 0.29, 1.34) | 0.00 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6111 |
| No | 282 | 2 | 0.7 | 277 | 2 | 0.7 | 0.9857 | 1.02 ( 0.14, 7.18) | 1.02 ( 0.14, 7.28) | 0.00 (-0.01, 0.01) | |
| Yes | 1719 | 18 | 1.0 | 1775 | 11 | 0.6 | 0.1639 | 0.59 ( 0.28, 1.25) | 0.59 ( 0.28, 1.25) | 0.00 (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.7899 |
| No | 229 | 1 | 0.4 | 250 | 1 | 0.4 | 0.9504 | 0.92 ( 0.06,14.56) | 0.92 ( 0.06,14.72) | 0.00 (-0.01, 0.01) | |
| Yes | 1772 | 19 | 1.1 | 1802 | 12 | 0.7 | 0.1903 | 0.62 ( 0.30, 1.28) | 0.62 ( 0.30, 1.28) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 15 | 0.7 | 2052 | 11 | 0.5 | 0.3945 | 0.72 | ( 0.33, 1.55) | 0.71 | ( 0.33, 1.56) | 0.00 | (-0.01,0.00) | |
| Sex | | | | | | | | | | | | | | 0.4571 |
| Male | 1065 | 12 | 1.1 | 1093 | 10 | 0.9 | 0.6243 | 0.81 | ( 0.35, 1.87) | 0.81 | ( 0.35, 1.88) | 0.00 | (-0.01,0.01) | |
| Female | 936 | 3 | 0.3 | 959 | 1 | 0.1 | 0.3052 | 0.33 | ( 0.03, 3.12) | 0.32 | ( 0.03, 3.13) | 0.00 | (-0.01,0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.4545 |
| <65 | 331 | 5 | 1.5 | 313 | 5 | 1.6 | 0.9290 | 1.06 | ( 0.31, 3.62) | 1.06 | ( 0.30, 3.69) | 0.00 | (-0.02,0.02) | |
| >=65 | 1670 | 10 | 0.6 | 1739 | 6 | 0.3 | 0.2785 | 0.58 | ( 0.21, 1.58) | 0.57 | ( 0.21, 1.58) | 0.00 | (-0.01,0.00) | |
| Region | | | | | | | | | | | | | | 0.9691 |
| North America | 273 | 4 | 1.5 | 273 | 4 | 1.5 | 1.0000 | 1.00 | ( 0.25, 3.96) | 1.00 | ( 0.25, 4.04) | 0.00 | (-0.02,0.02) | |
| Latin America | 511 | 3 | 0.6 | 504 | 2 | 0.4 | 0.6651 | 0.68 | ( 0.11, 4.03) | 0.67 | ( 0.11, 4.05) | 0.00 | (-0.01,0.01) | |
| Europe | 865 | 6 | 0.7 | 894 | 4 | 0.4 | 0.4923 | 0.65 | ( 0.18, 2.28) | 0.64 | ( 0.18, 2.29) | 0.00 | (-0.01,0.00) | |
| Asia | 231 | 1 | 0.4 | 248 | 0 | 0 | 0.4478 | 0.31 | ( 0.01, 7.59) | 0.31 | ( 0.01, 7.63) | 0.00 | (-0.02,0.01) | |
| Other | 121 | 1 | 0.8 | 133 | 1 | 0.8 | 0.9465 | 0.91 | ( 0.06, 14.39) | 0.91 | ( 0.06, 14.69) | 0.00 | (-0.02,0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7498 |
| Diabetic | 1045 | 13 | 1.2 | 1081 | 10 | 0.9 | 0.4773 | 0.74 | ( 0.33, 1.69) | 0.74 | ( 0.32, 1.70) | 0.00 | (-0.01,0.01) | |
| Non-Diabetic | 956 | 2 | 0.2 | 971 | 1 | 0.1 | 0.5543 | 0.49 | ( 0.04, 5.42) | 0.49 | ( 0.04, 5.43) | 0.00 | ( 0.00,0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2598 |
| <30 | 1086 | 6 | 0.6 | 1094 | 2 | 0.2 | 0.1535 | 0.33 | ( 0.07, 1.64) | 0.33 | ( 0.07, 1.64) | 0.00 | (-0.01,0.00) | |
| >=30 | 915 | 9 | 1.0 | 958 | 9 | 0.9 | 0.9220 | 0.96 | ( 0.38, 2.40) | 0.95 | ( 0.38, 2.42) | 0.00 | (-0.01,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8408 |
| <130 | 827 | 6 | 0.7 | 853 | 4 | 0.5 | 0.4943 | 0.65 | ( 0.18, 2.28) | 0.64 | ( 0.18, 2.29) | 0.00 | (-0.01,0.00) | |
| >=130 | 1174 | 9 | 0.8 | 1199 | 7 | 0.6 | 0.5864 | 0.76 | ( 0.28, 2.04) | 0.76 | ( 0.28, 2.05) | 0.00 | (-0.01,0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4711 |
| <75 | 935 | 7 | 0.7 | 934 | 6 | 0.6 | 0.7823 | 0.86 | ( 0.29, 2.54) | 0.86 | ( 0.29, 2.56) | 0.00 | (-0.01,0.01) | |
| 75 to <85 | 657 | 7 | 1.1 | 703 | 3 | 0.4 | 0.1683 | 0.40 | ( 0.10, 1.54) | 0.40 | ( 0.10, 1.55) | -0.01 | (-0.02,0.00) | |
| >=85 | 409 | 1 | 0.2 | 415 | 2 | 0.5 | 0.5715 | 1.97 | ( 0.18, 21.65) | 1.98 | ( 0.18, 21.87) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3143 |
| <30 | 161 | 1 | 0.6 | 148 | 3 | 2.0 | 0.2747 | 3.26 | ( 0.34, 31.03) | 3.31 | ( 0.34, 32.18) | 0.01 | (-0.01,0.04) | |
| 30 to <45 | 550 | 3 | 0.5 | 564 | 1 | 0.2 | 0.3044 | 0.33 | ( 0.03, 3.12) | 0.32 | ( 0.03, 3.12) | 0.00 | (-0.01,0.00) | |
| >=45 | 1289 | 11 | 0.9 | 1340 | 7 | 0.5 | 0.3036 | 0.61 | ( 0.24, 1.57) | 0.61 | ( 0.24, 1.58) | 0.00 | (-0.01,0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4705 |
| Normal (<30) | 764 | 2 | 0.3 | 787 | 3 | 0.4 | 0.6783 | 1.46 | ( 0.24, 8.69) | 1.46 | ( 0.24, 8.75) | 0.00 | ( 0.00,0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 4 | 0.4 | 938 | 4 | 0.4 | 0.9793 | 0.98 | ( 0.25, 3.91) | 0.98 | ( 0.24, 3.94) | 0.00 | (-0.01,0.01) | |
| Macroalbuminuria (>300) | 311 | 9 | 2.9 | 318 | 4 | 1.3 | 0.1493 | 0.43 | ( 0.14, 1.40) | 0.43 | ( 0.13, 1.40) | -0.02 | (-0.04,0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7835 |
| Low, moderate or high | 1477 | 10 | 0.7 | 1548 | 7 | 0.5 | 0.4083 | 0.67 | ( 0.25, 1.75) | 0.67 | ( 0.25, 1.76) | 0.00 | (-0.01,0.00) | |
| Very high | 519 | 5 | 1.0 | 495 | 4 | 0.8 | 0.7921 | 0.84 | ( 0.23, 3.11) | 0.84 | ( 0.22, 3.14) | 0.00 | (-0.01,0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7113 |
| No | 411 | 2 | 0.5 | 410 | 2 | 0.5 | 0.9981 | 1.00 | ( 0.14, 7.08) | 1.00 | ( 0.14, 7.15) | 0.00 | (-0.01,0.01) | |
| Yes | 1590 | 13 | 0.8 | 1642 | 9 | 0.5 | 0.3516 | 0.67 | ( 0.29, 1.56) | 0.67 | ( 0.28, 1.57) | 0.00 | (-0.01,0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4806 |
| No | 282 | 3 | 1.1 | 277 | 1 | 0.4 | 0.3243 | 0.34 | ( 0.04, 3.24) | 0.34 | ( 0.03, 3.26) | -0.01 | (-0.02,0.01) | |
| Yes | 1719 | 12 | 0.7 | 1775 | 10 | 0.6 | 0.6148 | 0.81 | ( 0.35, 1.86) | 0.81 | ( 0.35, 1.87) | 0.00 | (-0.01,0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5805 |
| No | 229 | 1 | 0.4 | 250 | 0 | 0 | 0.4406 | 0.31 | ( 0.01, 7.46) | 0.30 | ( 0.01, 7.50) | 0.00 | (-0.02,0.01) | |
| Yes | 1772 | 14 | 0.8 | 1802 | 11 | 0.6 | 0.5194 | 0.77 | ( 0.35, 1.70) | 0.77 | ( 0.35, 1.70) | 0.00 | (-0.01,0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 14 | 0.7 | 2052 | 16 | 0.8 | 0.7662 | 1.11 | ( 0.55, 2.28) | 1.12 | ( 0.54, 2.29) | 0.00 | ( 0.00,0.01) | |
| Sex | | | | | | | | | | | | | | 0.5283 |
| Male | 1065 | 10 | 0.9 | 1093 | 13 | 1.2 | 0.5711 | 1.27 | ( 0.56, 2.88) | 1.27 | ( 0.55, 2.91) | 0.00 | (-0.01,0.01) | |
| Female | 936 | 4 | 0.4 | 959 | 3 | 0.3 | 0.6812 | 0.73 | ( 0.16, 3.26) | 0.73 | ( 0.16, 3.28) | 0.00 | (-0.01,0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.9745 |
| <65 | 331 | 1 | 0.3 | 313 | 1 | 0.3 | 0.9684 | 1.06 | ( 0.07, 16.83) | 1.06 | ( 0.07, 16.98) | 0.00 | (-0.01,0.01) | |
| >=65 | 1670 | 13 | 0.8 | 1739 | 15 | 0.9 | 0.7856 | 1.11 | ( 0.53, 2.32) | 1.11 | ( 0.53, 2.34) | 0.00 | (-0.01,0.01) | |
| Region | | | | | | | | | | | | | | |
| North America | 273 | 2 | 0.7 | 273 | 3 | 1.1 | | | | | | | | |
| Latin America | 511 | 2 | 0.4 | 504 | 7 | 1.4 | | | | | | | | |
| Europe | 865 | 7 | 0.8 | 894 | 2 | 0.2 | | | | | | | | |
| Asia | 231 | 3 | 1.3 | 248 | 2 | 0.8 | | | | | | | | |
| Other | 121 | 0 | 0 | 133 | 2 | 1.5 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5060 |
| Diabetic | 1045 | 7 | 0.7 | 1081 | 10 | 0.9 | 0.5089 | 1.38 | ( 0.53, 3.61) | 1.38 | ( 0.53, 3.65) | 0.00 | ( 0.00,0.01) | |
| Non-Diabetic | 956 | 7 | 0.7 | 971 | 6 | 0.6 | 0.7593 | 0.84 | ( 0.28, 2.50) | 0.84 | ( 0.28, 2.52) | 0.00 | (-0.01,0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6393 |
| <30 | 1086 | 10 | 0.9 | 1094 | 10 | 0.9 | 0.9868 | 0.99 | ( 0.41, 2.38) | 0.99 | ( 0.41, 2.39) | 0.00 | (-0.01,0.01) | |
| >=30 | 915 | 4 | 0.4 | 958 | 6 | 0.6 | 0.5745 | 1.43 | ( 0.41, 5.06) | 1.44 | ( 0.40, 5.10) | 0.00 | ( 0.00,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6849 |
| <130 | 827 | 8 | 1.0 | 853 | 8 | 0.9 | 0.9504 | 0.97 | ( 0.37, 2.57) | 0.97 | ( 0.36, 2.59) | 0.00 | (-0.01,0.01) | |
| >=130 | 1174 | 6 | 0.5 | 1199 | 8 | 0.7 | 0.6195 | 1.31 | ( 0.45, 3.75) | 1.31 | ( 0.45, 3.78) | 0.00 | ( 0.00,0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8620 |
| <75 | 935 | 10 | 1.1 | 934 | 10 | 1.1 | 0.9981 | 1.00 | ( 0.42, 2.39) | 1.00 | ( 0.41, 2.42) | 0.00 | (-0.01,0.01) | |
| 75 to <85 | 657 | 3 | 0.5 | 703 | 4 | 0.6 | 0.7723 | 1.25 | ( 0.28, 5.55) | 1.25 | ( 0.28, 5.60) | 0.00 | (-0.01,0.01) | |
| >=85 | 409 | 1 | 0.2 | 415 | 2 | 0.5 | 0.5715 | 1.97 | ( 0.18, 21.65) | 1.98 | ( 0.18, 21.87) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7756 |
| <30 | 161 | 2 | 1.2 | 148 | 3 | 2.0 | 0.5849 | 1.63 | ( 0.28, 9.63) | 1.64 | ( 0.27, 9.98) | 0.01 | (-0.02,0.04) | |
| 30 to <45 | 550 | 4 | 0.7 | 564 | 3 | 0.5 | 0.6799 | 0.73 | ( 0.16, 3.25) | 0.73 | ( 0.16, 3.28) | 0.00 | (-0.01,0.01) | |
| >=45 | 1289 | 8 | 0.6 | 1340 | 10 | 0.7 | 0.6962 | 1.20 | ( 0.48, 3.04) | 1.20 | ( 0.47, 3.06) | 0.00 | (-0.01,0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3641 |
| Normal (<30) | 764 | 4 | 0.5 | 787 | 2 | 0.3 | 0.3928 | 0.49 | ( 0.09, 2.64) | 0.48 | ( 0.09, 2.65) | 0.00 | (-0.01,0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 8 | 0.9 | 938 | 13 | 1.4 | 0.2913 | 1.60 | ( 0.66, 3.83) | 1.60 | ( 0.66, 3.89) | 0.01 | ( 0.00,0.01) | |
| Macroalbuminuria (>300) | 311 | 2 | 0.6 | 318 | 1 | 0.3 | 0.5498 | 0.49 | ( 0.04, 5.37) | 0.49 | ( 0.04, 5.40) | 0.00 | (-0.01,0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8625 |
| Low, moderate or high | 1477 | 8 | 0.5 | 1548 | 10 | 0.6 | 0.7091 | 1.19 | ( 0.47, 3.01) | 1.19 | ( 0.47, 3.03) | 0.00 | ( 0.00,0.01) | |
| Very high | 519 | 6 | 1.2 | 495 | 6 | 1.2 | 0.9342 | 1.05 | ( 0.34, 3.23) | 1.05 | ( 0.34, 3.27) | 0.00 | (-0.01,0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1741 |
| No | 411 | 7 | 1.7 | 410 | 4 | 1.0 | 0.3646 | 0.57 | ( 0.17, 1.94) | 0.57 | ( 0.17, 1.96) | -0.01 | (-0.02,0.01) | |
| Yes | 1590 | 7 | 0.4 | 1642 | 12 | 0.7 | 0.2800 | 1.66 | ( 0.66, 4.21) | 1.66 | ( 0.65, 4.24) | 0.00 | ( 0.00,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3325 |
| No | 282 | 6 | 2.1 | 277 | 4 | 1.4 | 0.5421 | 0.68 | ( 0.19, 2.38) | 0.67 | ( 0.19, 2.41) | -0.01 | (-0.03,0.02) | |
| Yes | 1719 | 8 | 0.5 | 1775 | 12 | 0.7 | 0.4092 | 1.45 | ( 0.60, 3.55) | 1.46 | ( 0.59, 3.57) | 0.00 | ( 0.00,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1250 |
| No | 229 | 3 | 1.3 | 250 | 0 | 0 | 0.1106 | 0.13 | (<0.01, 2.52) | 0.13 | (<0.01, 2.51) | -0.01 | (-0.03,0.00) | |
| Yes | 1772 | 11 | 0.6 | 1802 | 16 | 0.9 | 0.3564 | 1.43 | ( 0.67, 3.07) | 1.43 | ( 0.66, 3.10) | 0.00 | ( 0.00,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 2 | 0.1 | 2052 | 3 | 0.1 | 0.6749 | 1.46 | ( 0.24, 8.74) | 1.46 | ( 0.24, 8.77) | 0.00 ( 0.00,0.00) | |
| Sex | | | | | | | | | | | | | |
| Male | 1065 | 1 | 0.1 | 1093 | 1 | 0.1 | | | | | | | |
| Female | 936 | 1 | 0.1 | 959 | 2 | 0.2 | | | | | | | |
| Age [years] | | | | | | | | | | | | | |
| <65 | 331 | 2 | 0.6 | 313 | 0 | 0 | | | | | | | |
| >=65 | 1670 | 0 | 0 | 1739 | 3 | 0.2 | | | | | | | |
| Region | | | | | | | | | | | | | |
| North America | 273 | 0 | 0 | 273 | 1 | 0.4 | | | | | | | |
| Latin America | 511 | 0 | 0 | 504 | 0 | 0 | | | | | | | |
| Europe | 865 | 0 | 0 | 894 | 1 | 0.1 | | | | | | | |
| Asia | 231 | 1 | 0.4 | 248 | 0 | 0 | | | | | | | |
| Other | 121 | 1 | 0.8 | 133 | 1 | 0.8 | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | |
| Diabetic | 1045 | 2 | 0.2 | 1081 | 3 | 0.3 | | | | | | | |
| Non-Diabetic | 956 | 0 | 0 | 971 | 0 | 0 | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | |
| <30 | 1086 | 1 | 0.1 | 1094 | 1 | 0.1 | | | | | | | |
| >=30 | 915 | 1 | 0.1 | 958 | 2 | 0.2 | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | |
| <130 | 827 | 1 | 0.1 | 853 | 0 | 0 | | | | | | | |
| >=130 | 1174 | 1 | 0.1 | 1199 | 3 | 0.3 | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | |
| <75 | 935 | 0 | 0 | 934 | 1 | 0.1 | | | | | | | |
| 75 to <85 | 657 | 1 | 0.2 | 703 | 2 | 0.3 | | | | | | | |
| >=85 | 409 | 1 | 0.2 | 415 | 0 | 0 | | | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 161 | 1 | 0.6 | 148 | 1 | 0.7 | | | | | |
| 30 to <45 | 550 | 0 | 0 | 564 | 1 | 0.2 | | | | | |
| >=45 | 1289 | 1 | 0.1 | 1340 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 764 | 0 | 0 | 787 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 2 | 0.2 | 938 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 311 | 0 | 0 | 318 | 3 | 0.9 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1477 | 1 | 0.1 | 1548 | 1 | 0.1 | | | | | |
| Very high | 519 | 1 | 0.2 | 495 | 2 | 0.4 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 411 | 1 | 0.2 | 410 | 0 | 0 | | | | | |
| Yes | 1590 | 1 | 0.1 | 1642 | 3 | 0.2 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 282 | 0 | 0 | 277 | 0 | 0 | | | | | |
| Yes | 1719 | 2 | 0.1 | 1775 | 3 | 0.2 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 229 | 1 | 0.4 | 250 | 1 | 0.4 | | | | | |
| Yes | 1772 | 1 | 0.1 | 1802 | 2 | 0.1 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 6 | 0.3 | 2052 | 8 | 0.4 | 0.6253 | 1.30 ( 0.45, 3.74) | 1.30 ( 0.45, 3.76) | 0.00 ( 0.00,0.00) | |
| Sex | | | | | | | | | | | |
| Male | 1065 | 5 | 0.5 | 1093 | 2 | 0.2 | | | | | |
| Female | 936 | 1 | 0.1 | 959 | 6 | 0.6 | | | | | |
| Age [years] | | | | | | | | | | | 0.8752 |
| <65 | 331 | 1 | 0.3 | 313 | 1 | 0.3 | 0.9684 | 1.06 ( 0.07, 16.83) | 1.06 ( 0.07, 16.98) | 0.00 (-0.01,0.01) | |
| >=65 | 1670 | 5 | 0.3 | 1739 | 7 | 0.4 | 0.6113 | 1.34 ( 0.43, 4.23) | 1.35 ( 0.43, 4.25) | 0.00 ( 0.00,0.00) | |
| Region | | | | | | | | | | | |
| North America | 273 | 0 | 0 | 273 | 1 | 0.4 | | | | | |
| Latin America | 511 | 2 | 0.4 | 504 | 2 | 0.4 | | | | | |
| Europe | 865 | 2 | 0.2 | 894 | 3 | 0.3 | | | | | |
| Asia | 231 | 0 | 0 | 248 | 1 | 0.4 | | | | | |
| Other | 121 | 2 | 1.7 | 133 | 1 | 0.8 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | 0.5765 |
| Diabetic | 1045 | 6 | 0.6 | 1081 | 7 | 0.6 | 0.8282 | 1.13 ( 0.38, 3.34) | 1.13 ( 0.38, 3.37) | 0.00 (-0.01,0.01) | |
| Non-Diabetic | 956 | 0 | 0 | 971 | 1 | 0.1 | 0.4861 | 2.95 ( 0.12, 72.42) | 2.96 ( 0.12, 72.67) | 0.00 ( 0.00,0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.7576 |
| <30 | 1086 | 2 | 0.2 | 1094 | 2 | 0.2 | 0.9941 | 0.99 ( 0.14, 7.03) | 0.99 ( 0.14, 7.06) | 0.00 ( 0.00,0.00) | |
| >=30 | 915 | 4 | 0.4 | 958 | 6 | 0.6 | 0.5745 | 1.43 ( 0.41, 5.06) | 1.44 ( 0.40, 5.10) | 0.00 ( 0.00,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 827 | 3 | 0.4 | 853 | 3 | 0.4 | | | | | |
| >=130 | 1174 | 3 | 0.3 | 1199 | 5 | 0.4 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 935 | 3 | 0.3 | 934 | 3 | 0.3 | | | | | |
| 75 to <85 | 657 | 3 | 0.5 | 703 | 4 | 0.6 | | | | | |
| >=85 | 409 | 0 | 0 | 415 | 1 | 0.2 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 161 | 1 | 0.6 | 148 | 3 | 2.0 | | | | | | |
| 30 to <45 | 550 | 1 | 0.2 | 564 | 3 | 0.5 | | | | | | |
| >=45 | 1289 | 4 | 0.3 | 1340 | 2 | 0.1 | | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 764 | 1 | 0.1 | 787 | 3 | 0.4 | | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 3 | 0.3 | 938 | 2 | 0.2 | | | | | | |
| Macroalbuminuria (>300) | 311 | 2 | 0.6 | 318 | 3 | 0.9 | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | |
| Low, moderate or high | 1477 | 2 | 0.1 | 1548 | 3 | 0.2 | | | | | | |
| Very high | 519 | 4 | 0.8 | 495 | 5 | 1.0 | | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | |
| No | 411 | 1 | 0.2 | 410 | 4 | 1.0 | | | | | | |
| Yes | 1590 | 5 | 0.3 | 1642 | 4 | 0.2 | | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5638 |
| No | 282 | 0 | 0 | 277 | 1 | 0.4 | 0.4709 | 3.05 ( 0.12, 74.65) | 3.07 ( 0.12, 75.56) | 0.00 (-0.01,0.01) | | |
| Yes | 1719 | 6 | 0.3 | 1775 | 7 | 0.4 | 0.8259 | 1.13 ( 0.38, 3.36) | 1.13 ( 0.38, 3.37) | 0.00 ( 0.00,0.00) | | |
| Baseline use of diuretics | | | | | | | | | | | | 0.8625 |
| No | 229 | 0 | 0 | 250 | 0 | 0 | 0.9651 | 0.92 ( 0.02, 45.99) | 0.92 ( 0.02, 46.36) | 0.00 (-0.01,0.01) | | |
| Yes | 1772 | 6 | 0.3 | 1802 | 8 | 0.4 | 0.6142 | 1.31 ( 0.46, 3.77) | 1.31 ( 0.45, 3.79) | 0.00 ( 0.00,0.01) | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 19 | 0.9 | 2052 | 29 | 1.4 | 0.1724 | 1.49 | ( 0.84, 2.65) | 1.50 | ( 0.84, 2.68) | 0.00 | ( 0.00,0.01) | |
| Sex | | | | | | | | | | | | | | 0.1697 |
| Male | 1065 | 13 | 1.2 | 1093 | 14 | 1.3 | 0.8999 | 1.05 | ( 0.50, 2.22) | 1.05 | ( 0.49, 2.24) | 0.00 | (-0.01,0.01) | |
| Female | 936 | 6 | 0.6 | 959 | 15 | 1.6 | 0.0550 | 2.44 | ( 0.95, 6.26) | 2.46 | ( 0.95, 6.38) | 0.01 | ( 0.00,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.6597 |
| <65 | 331 | 2 | 0.6 | 313 | 4 | 1.3 | 0.3738 | 2.12 | ( 0.39, 11.47) | 2.13 | ( 0.39, 11.71) | 0.01 | (-0.01,0.02) | |
| >=65 | 1670 | 17 | 1.0 | 1739 | 25 | 1.4 | 0.2669 | 1.41 | ( 0.77, 2.61) | 1.42 | ( 0.76, 2.64) | 0.00 | ( 0.00,0.01) | |
| Region | | | | | | | | | | | | | | 0.5235 |
| North America | 273 | 4 | 1.5 | 273 | 8 | 2.9 | 0.2430 | 2.00 | ( 0.61, 6.56) | 2.03 | ( 0.60, 6.82) | 0.01 | (-0.01,0.04) | |
| Latin America | 511 | 5 | 1.0 | 504 | 11 | 2.2 | 0.1236 | 2.23 | ( 0.78, 6.37) | 2.26 | ( 0.78, 6.55) | 0.01 | ( 0.00,0.03) | |
| Europe | 865 | 8 | 0.9 | 894 | 7 | 0.8 | 0.7463 | 0.85 | ( 0.31, 2.32) | 0.85 | ( 0.31, 2.34) | 0.00 | (-0.01,0.01) | |
| Asia | 231 | 1 | 0.4 | 248 | 0 | 0 | 0.4478 | 0.31 | ( 0.01, 7.59) | 0.31 | ( 0.01, 7.63) | 0.00 | (-0.02,0.01) | |
| Other | 121 | 1 | 0.8 | 133 | 3 | 2.3 | 0.3608 | 2.73 | ( 0.29, 25.89) | 2.77 | ( 0.28, 26.99) | 0.01 | (-0.02,0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7039 |
| Diabetic | 1045 | 10 | 1.0 | 1081 | 17 | 1.6 | 0.2050 | 1.64 | ( 0.76, 3.57) | 1.65 | ( 0.75, 3.63) | 0.01 | ( 0.00,0.02) | |
| Non-Diabetic | 956 | 9 | 0.9 | 971 | 12 | 1.2 | 0.5337 | 1.31 | ( 0.56, 3.10) | 1.32 | ( 0.55, 3.14) | 0.00 | (-0.01,0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3470 |
| <30 | 1086 | 10 | 0.9 | 1094 | 11 | 1.0 | 0.8396 | 1.09 | ( 0.47, 2.56) | 1.09 | ( 0.46, 2.58) | 0.00 | (-0.01,0.01) | |
| >=30 | 915 | 9 | 1.0 | 958 | 18 | 1.9 | 0.1042 | 1.91 | ( 0.86, 4.23) | 1.93 | ( 0.86, 4.31) | 0.01 | ( 0.00,0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2601 |
| <130 | 827 | 10 | 1.2 | 853 | 20 | 2.3 | 0.0789 | 1.94 | ( 0.91, 4.12) | 1.96 | ( 0.91, 4.22) | 0.01 | ( 0.00,0.02) | |
| >=130 | 1174 | 9 | 0.8 | 1199 | 9 | 0.8 | 0.9642 | 0.98 | ( 0.39, 2.46) | 0.98 | ( 0.39, 2.47) | 0.00 | (-0.01,0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9826 |
| <75 | 935 | 10 | 1.1 | 934 | 15 | 1.6 | 0.3128 | 1.50 | ( 0.68, 3.33) | 1.51 | ( 0.67, 3.38) | 0.01 | (-0.01,0.02) | |
| 75 to <85 | 657 | 6 | 0.9 | 703 | 10 | 1.4 | 0.3841 | 1.56 | ( 0.57, 4.26) | 1.57 | ( 0.57, 4.33) | 0.01 | (-0.01,0.02) | |
| >=85 | 409 | 3 | 0.7 | 415 | 4 | 1.0 | 0.7187 | 1.31 | ( 0.30, 5.83) | 1.32 | ( 0.29, 5.92) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2358 |
| <30 | 161 | 5 | 3.1 | 148 | 3 | 2.0 | 0.5509 | 0.65 | ( 0.16, 2.68) | 0.65 | ( 0.15, 2.75) | -0.01 | (-0.05,0.02) | |
| 30 to <45 | 550 | 6 | 1.1 | 564 | 16 | 2.8 | 0.0363 | 2.60 | ( 1.03, 6.60) | 2.65 | ( 1.03, 6.82) | 0.02 | ( 0.00,0.03) | |
| >=45 | 1289 | 8 | 0.6 | 1340 | 10 | 0.7 | 0.6962 | 1.20 | ( 0.48, 3.04) | 1.20 | ( 0.47, 3.06) | 0.00 | (-0.01,0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1589 |
| Normal (<30) | 764 | 5 | 0.7 | 787 | 13 | 1.7 | 0.0667 | 2.52 | ( 0.90, 7.05) | 2.55 | ( 0.90, 7.19) | 0.01 | ( 0.00,0.02) | |
| Microalbuminuria (30 to <=300) | 921 | 12 | 1.3 | 938 | 10 | 1.1 | 0.6368 | 0.82 | ( 0.36, 1.88) | 0.82 | ( 0.35, 1.90) | 0.00 | (-0.01,0.01) | |
| Macroalbuminuria (>300) | 311 | 2 | 0.6 | 318 | 6 | 1.9 | 0.1640 | 2.93 | ( 0.60, 14.43) | 2.97 | ( 0.60, 14.83) | 0.01 | ( 0.00,0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7288 |
| Low, moderate or high | 1477 | 11 | 0.7 | 1548 | 16 | 1.0 | 0.3985 | 1.39 | ( 0.65, 2.98) | 1.39 | ( 0.64, 3.01) | 0.00 | ( 0.00,0.01) | |
| Very high | 519 | 8 | 1.5 | 495 | 13 | 2.6 | 0.2253 | 1.70 | ( 0.71, 4.08) | 1.72 | ( 0.71, 4.19) | 0.01 | (-0.01,0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1475 |
| No | 411 | 3 | 0.7 | 410 | 10 | 2.4 | 0.0498 | 3.34 | ( 0.93, 12.05) | 3.40 | ( 0.93, 12.45) | 0.02 | ( 0.00,0.03) | |
| Yes | 1590 | 16 | 1.0 | 1642 | 19 | 1.2 | 0.6787 | 1.15 | ( 0.59, 2.23) | 1.15 | ( 0.59, 2.25) | 0.00 | (-0.01,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4851 |
| No | 282 | 2 | 0.7 | 277 | 5 | 1.8 | 0.2441 | 2.55 | ( 0.50, 13.01) | 2.57 | ( 0.50, 13.38) | 0.01 | (-0.01,0.03) | |
| Yes | 1719 | 17 | 1.0 | 1775 | 24 | 1.4 | 0.3190 | 1.37 | ( 0.74, 2.54) | 1.37 | ( 0.73, 2.56) | 0.00 | ( 0.00,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3157 |
| No | 229 | 2 | 0.9 | 250 | 1 | 0.4 | 0.5118 | 0.46 | ( 0.04, 5.02) | 0.46 | ( 0.04, 5.06) | 0.00 | (-0.02,0.01) | |
| Yes | 1772 | 17 | 1.0 | 1802 | 28 | 1.6 | 0.1110 | 1.62 | ( 0.89, 2.95) | 1.63 | ( 0.89, 2.99) | 0.01 | ( 0.00,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 2 | 0.1 | 2052 | 1 | <0.1 | 0.5489 | 0.49 | ( 0.04, 5.37) | 0.49 | ( 0.04, 5.38) | 0.00 ( 0.00,0.00) | |
| Sex | | | | | | | | | | | | | |
| Male | 1065 | 2 | 0.2 | 1093 | 1 | 0.1 | | | | | | | |
| Female | 936 | 0 | 0 | 959 | 0 | 0 | | | | | | | |
| Age [years] | | | | | | | | | | | | | |
| <65 | 331 | 0 | 0 | 313 | 0 | 0 | | | | | | | |
| >=65 | 1670 | 2 | 0.1 | 1739 | 1 | 0.1 | | | | | | | |
| Region | | | | | | | | | | | | | |
| North America | 273 | 0 | 0 | 273 | 1 | 0.4 | | | | | | | |
| Latin America | 511 | 0 | 0 | 504 | 0 | 0 | | | | | | | |
| Europe | 865 | 2 | 0.2 | 894 | 0 | 0 | | | | | | | |
| Asia | 231 | 0 | 0 | 248 | 0 | 0 | | | | | | | |
| Other | 121 | 0 | 0 | 133 | 0 | 0 | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | |
| Diabetic | 1045 | 1 | 0.1 | 1081 | 0 | 0 | | | | | | | |
| Non-Diabetic | 956 | 1 | 0.1 | 971 | 1 | 0.1 | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | |
| <30 | 1086 | 1 | 0.1 | 1094 | 0 | 0 | | | | | | | |
| >=30 | 915 | 1 | 0.1 | 958 | 1 | 0.1 | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | |
| <130 | 827 | 1 | 0.1 | 853 | 1 | 0.1 | | | | | | | |
| >=130 | 1174 | 1 | 0.1 | 1199 | 0 | 0 | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | |
| <75 | 935 | 2 | 0.2 | 934 | 1 | 0.1 | | | | | | | |
| 75 to <85 | 657 | 0 | 0 | 703 | 0 | 0 | | | | | | | |
| >=85 | 409 | 0 | 0 | 415 | 0 | 0 | | | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 161 | 0 | 0 | 148 | 0 | 0 | | | | | |
| 30 to <45 | 550 | 1 | 0.2 | 564 | 0 | 0 | | | | | |
| >=45 | 1289 | 1 | 0.1 | 1340 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 764 | 0 | 0 | 787 | 1 | 0.1 | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 1 | 0.1 | 938 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 311 | 1 | 0.3 | 318 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1477 | 1 | 0.1 | 1548 | 1 | 0.1 | | | | | |
| Very high | 519 | 1 | 0.2 | 495 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 411 | 1 | 0.2 | 410 | 0 | 0 | | | | | |
| Yes | 1590 | 1 | 0.1 | 1642 | 1 | 0.1 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 282 | 0 | 0 | 277 | 0 | 0 | | | | | |
| Yes | 1719 | 2 | 0.1 | 1775 | 1 | 0.1 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 229 | 0 | 0 | 250 | 0 | 0 | | | | | |
| Yes | 1772 | 2 | 0.1 | 1802 | 1 | 0.1 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 11 | 0.5 | 2052 | 13 | 0.6 | 0.7281 | 1.15 | ( 0.52, 2.57) | 1.15 | ( 0.52, 2.58) | 0.00 | ( 0.00,0.01) | |
| Sex | | | | | | | | | | | | | | 0.3920 |
| Male | 1065 | 7 | 0.7 | 1093 | 6 | 0.5 | 0.7451 | 0.84 | ( 0.28, 2.48) | 0.83 | ( 0.28, 2.49) | 0.00 | (-0.01,0.01) | |
| Female | 936 | 4 | 0.4 | 959 | 7 | 0.7 | 0.3860 | 1.71 | ( 0.50, 5.82) | 1.71 | ( 0.50, 5.87) | 0.00 | ( 0.00,0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.9536 |
| <65 | 331 | 1 | 0.3 | 313 | 1 | 0.3 | 0.9684 | 1.06 | ( 0.07, 16.83) | 1.06 | ( 0.07, 16.98) | 0.00 | (-0.01,0.01) | |
| >=65 | 1670 | 10 | 0.6 | 1739 | 12 | 0.7 | 0.7394 | 1.15 | ( 0.50, 2.66) | 1.15 | ( 0.50, 2.68) | 0.00 | ( 0.00,0.01) | |
| Region | | | | | | | | | | | | | | 0.5700 |
| North America | 273 | 1 | 0.4 | 273 | 4 | 1.5 | 0.1777 | 4.00 | ( 0.45, 35.56) | 4.04 | ( 0.45, 36.42) | 0.01 | ( 0.00,0.03) | |
| Latin America | 511 | 2 | 0.4 | 504 | 3 | 0.6 | 0.6428 | 1.52 | ( 0.26, 9.06) | 1.52 | ( 0.25, 9.16) | 0.00 | (-0.01,0.01) | |
| Europe | 865 | 6 | 0.7 | 894 | 4 | 0.4 | 0.4923 | 0.65 | ( 0.18, 2.28) | 0.64 | ( 0.18, 2.29) | 0.00 | (-0.01,0.00) | |
| Asia | 231 | 1 | 0.4 | 248 | 0 | 0 | 0.4478 | 0.31 | ( 0.01, 7.59) | 0.31 | ( 0.01, 7.63) | 0.00 | (-0.02,0.01) | |
| Other | 121 | 1 | 0.8 | 133 | 2 | 1.5 | 0.6178 | 1.82 | ( 0.17, 19.81) | 1.83 | ( 0.16, 20.46) | 0.01 | (-0.02,0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4445 |
| Diabetic | 1045 | 5 | 0.5 | 1081 | 8 | 0.7 | 0.4392 | 1.55 | ( 0.51, 4.71) | 1.55 | ( 0.51, 4.76) | 0.00 | ( 0.00,0.01) | |
| Non-Diabetic | 956 | 6 | 0.6 | 971 | 5 | 0.5 | 0.7427 | 0.82 | ( 0.25, 2.68) | 0.82 | ( 0.25, 2.69) | 0.00 | (-0.01,0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1240 |
| <30 | 1086 | 7 | 0.6 | 1094 | 4 | 0.4 | 0.3581 | 0.57 | ( 0.17, 1.93) | 0.57 | ( 0.17, 1.94) | 0.00 | (-0.01,0.00) | |
| >=30 | 915 | 4 | 0.4 | 958 | 9 | 0.9 | 0.1906 | 2.15 | ( 0.66, 6.95) | 2.16 | ( 0.66, 7.04) | 0.01 | ( 0.00,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4670 |
| <130 | 827 | 6 | 0.7 | 853 | 9 | 1.1 | 0.4728 | 1.45 | ( 0.52, 4.07) | 1.46 | ( 0.52, 4.12) | 0.00 | (-0.01,0.01) | |
| >=130 | 1174 | 5 | 0.4 | 1199 | 4 | 0.3 | 0.7146 | 0.78 | ( 0.21, 2.91) | 0.78 | ( 0.21, 2.92) | 0.00 | (-0.01,0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6768 |
| <75 | 935 | 6 | 0.6 | 934 | 5 | 0.5 | 0.7637 | 0.83 | ( 0.26, 2.72) | 0.83 | ( 0.25, 2.74) | 0.00 | (-0.01,0.01) | |
| 75 to <85 | 657 | 3 | 0.5 | 703 | 6 | 0.9 | 0.3670 | 1.87 | ( 0.47, 7.44) | 1.88 | ( 0.47, 7.53) | 0.00 | ( 0.00,0.01) | |
| >=85 | 409 | 2 | 0.5 | 415 | 2 | 0.5 | 0.9884 | 0.99 | ( 0.14, 6.96) | 0.99 | ( 0.14, 7.03) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5764 |
| <30 | 161 | 4 | 2.5 | 148 | 2 | 1.4 | 0.4708 | 0.54 | ( 0.10, 2.93) | 0.54 | ( 0.10, 2.98) | -0.01 | (-0.04,0.02) | |
| 30 to <45 | 550 | 4 | 0.7 | 564 | 6 | 1.1 | 0.5515 | 1.46 | ( 0.42, 5.16) | 1.47 | ( 0.41, 5.23) | 0.00 | (-0.01,0.01) | |
| >=45 | 1289 | 3 | 0.2 | 1340 | 5 | 0.4 | 0.5135 | 1.60 | ( 0.38, 6.69) | 1.61 | ( 0.38, 6.73) | 0.00 | ( 0.00,0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6391 |
| Normal (<30) | 764 | 3 | 0.4 | 787 | 6 | 0.8 | 0.3379 | 1.94 | ( 0.49, 7.74) | 1.95 | ( 0.49, 7.82) | 0.00 | ( 0.00,0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 6 | 0.7 | 938 | 5 | 0.5 | 0.7393 | 0.82 | ( 0.25, 2.67) | 0.82 | ( 0.25, 2.69) | 0.00 | (-0.01,0.01) | |
| Macroalbuminuria (>300) | 311 | 2 | 0.6 | 318 | 2 | 0.6 | 0.9822 | 0.98 | ( 0.14, 6.90) | 0.98 | ( 0.14, 6.99) | 0.00 | (-0.01,0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4581 |
| Low, moderate or high | 1477 | 4 | 0.3 | 1548 | 7 | 0.5 | 0.4074 | 1.67 | ( 0.49, 5.69) | 1.67 | ( 0.49, 5.73) | 0.00 | ( 0.00,0.01) | |
| Very high | 519 | 7 | 1.3 | 495 | 6 | 1.2 | 0.8467 | 0.90 | ( 0.30, 2.66) | 0.90 | ( 0.30, 2.69) | 0.00 | (-0.02,0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7425 |
| No | 411 | 2 | 0.5 | 410 | 3 | 0.7 | 0.6518 | 1.50 | ( 0.25, 8.95) | 1.51 | ( 0.25, 9.07) | 0.00 | (-0.01,0.01) | |
| Yes | 1590 | 9 | 0.6 | 1642 | 10 | 0.6 | 0.8731 | 1.08 | ( 0.44, 2.64) | 1.08 | ( 0.44, 2.66) | 0.00 | ( 0.00,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4491 |
| No | 282 | 2 | 0.7 | 277 | 4 | 1.4 | 0.3992 | 2.04 | ( 0.38, 11.03) | 2.05 | ( 0.37, 11.29) | 0.01 | (-0.01,0.02) | |
| Yes | 1719 | 9 | 0.5 | 1775 | 9 | 0.5 | 0.9456 | 0.97 | ( 0.39, 2.43) | 0.97 | ( 0.38, 2.45) | 0.00 | ( 0.00,0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3951 |
| No | 229 | 1 | 0.4 | 250 | 0 | 0 | 0.4406 | 0.31 | ( 0.01, 7.46) | 0.30 | ( 0.01, 7.50) | 0.00 | (-0.02,0.01) | |
| Yes | 1772 | 10 | 0.6 | 1802 | 13 | 0.7 | 0.5571 | 1.28 | ( 0.56, 2.91) | 1.28 | ( 0.56, 2.93) | 0.00 | ( 0.00,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 24 | 1.2 | 2052 | 33 | 1.6 | 0.2692 | 1.34 | ( 0.80, 2.26) | 1.35 | ( 0.79, 2.29) | 0.00 | ( 0.00,0.01) | |
| Sex | | | | | | | | | | | | | | 0.3769 |
| Male | 1065 | 13 | 1.2 | 1093 | 14 | 1.3 | 0.8999 | 1.05 | ( 0.50, 2.22) | 1.05 | ( 0.49, 2.24) | 0.00 | (-0.01,0.01) | |
| Female | 936 | 11 | 1.2 | 959 | 19 | 2.0 | 0.1599 | 1.69 | ( 0.81, 3.52) | 1.70 | ( 0.80, 3.59) | 0.01 | ( 0.00,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.7623 |
| <65 | 331 | 3 | 0.9 | 313 | 3 | 1.0 | 0.9451 | 1.06 | ( 0.22, 5.20) | 1.06 | ( 0.21, 5.28) | 0.00 | (-0.01,0.02) | |
| >=65 | 1670 | 21 | 1.3 | 1739 | 30 | 1.7 | 0.2609 | 1.37 | ( 0.79, 2.39) | 1.38 | ( 0.79, 2.42) | 0.00 | ( 0.00,0.01) | |
| Region | | | | | | | | | | | | | | 0.9395 |
| North America | 273 | 7 | 2.6 | 273 | 7 | 2.6 | 1.0000 | 1.00 | ( 0.36, 2.81) | 1.00 | ( 0.35, 2.89) | 0.00 | (-0.03,0.03) | |
| Latin America | 511 | 3 | 0.6 | 504 | 6 | 1.2 | 0.3052 | 2.03 | ( 0.51, 8.06) | 2.04 | ( 0.51, 8.20) | 0.01 | (-0.01,0.02) | |
| Europe | 865 | 7 | 0.8 | 894 | 11 | 1.2 | 0.3802 | 1.52 | ( 0.59, 3.90) | 1.53 | ( 0.59, 3.96) | 0.00 | (-0.01,0.01) | |
| Asia | 231 | 3 | 1.3 | 248 | 4 | 1.6 | 0.7746 | 1.24 | ( 0.28, 5.49) | 1.25 | ( 0.28, 5.63) | 0.00 | (-0.02,0.02) | |
| Other | 121 | 4 | 3.3 | 133 | 5 | 3.8 | 0.8452 | 1.14 | ( 0.31, 4.14) | 1.14 | ( 0.30, 4.36) | 0.00 | (-0.04,0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0665 |
| Diabetic | 1045 | 10 | 1.0 | 1081 | 22 | 2.0 | 0.0412 | 2.13 | ( 1.01, 4.47) | 2.15 | ( 1.01, 4.56) | 0.01 | ( 0.00,0.02) | |
| Non-Diabetic | 956 | 14 | 1.5 | 971 | 11 | 1.1 | 0.5201 | 0.77 | ( 0.35, 1.70) | 0.77 | ( 0.35, 1.71) | 0.00 | (-0.01,0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6588 |
| <30 | 1086 | 14 | 1.3 | 1094 | 17 | 1.6 | 0.6016 | 1.21 | ( 0.60, 2.43) | 1.21 | ( 0.59, 2.46) | 0.00 | (-0.01,0.01) | |
| >=30 | 915 | 10 | 1.1 | 958 | 16 | 1.7 | 0.2858 | 1.53 | ( 0.70, 3.35) | 1.54 | ( 0.69, 3.41) | 0.01 | ( 0.00,0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7187 |
| <130 | 827 | 12 | 1.5 | 853 | 15 | 1.8 | 0.6163 | 1.21 | ( 0.57, 2.57) | 1.22 | ( 0.57, 2.61) | 0.00 | (-0.01,0.02) | |
| >=130 | 1174 | 12 | 1.0 | 1199 | 18 | 1.5 | 0.2963 | 1.47 | ( 0.71, 3.04) | 1.48 | ( 0.71, 3.08) | 0.00 | ( 0.00,0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5877 |
| <75 | 935 | 16 | 1.7 | 934 | 18 | 1.9 | 0.7269 | 1.13 | ( 0.58, 2.19) | 1.13 | ( 0.57, 2.23) | 0.00 | (-0.01,0.01) | |
| 75 to <85 | 657 | 6 | 0.9 | 703 | 13 | 1.8 | 0.1417 | 2.02 | ( 0.77, 5.30) | 2.04 | ( 0.77, 5.41) | 0.01 | ( 0.00,0.02) | |
| >=85 | 409 | 2 | 0.5 | 415 | 2 | 0.5 | 0.9884 | 0.99 | ( 0.14, 6.96) | 0.99 | ( 0.14, 7.03) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3749 |
| <30 | 161 | 1 | 0.6 | 148 | 5 | 3.4 | 0.0793 | 5.44 | ( 0.64, 46.02) | 5.59 | ( 0.65, 48.45) | 0.03 | ( 0.00,0.06) | |
| 30 to <45 | 550 | 11 | 2.0 | 564 | 12 | 2.1 | 0.8809 | 1.06 | ( 0.47, 2.39) | 1.07 | ( 0.47, 2.43) | 0.00 | (-0.02,0.02) | |
| >=45 | 1289 | 12 | 0.9 | 1340 | 16 | 1.2 | 0.5112 | 1.28 | ( 0.61, 2.70) | 1.29 | ( 0.61, 2.73) | 0.00 | (-0.01,0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8681 |
| Normal (<30) | 764 | 7 | 0.9 | 787 | 10 | 1.3 | 0.5027 | 1.39 | ( 0.53, 3.62) | 1.39 | ( 0.53, 3.68) | 0.00 | (-0.01,0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 13 | 1.4 | 938 | 17 | 1.8 | 0.4928 | 1.28 | ( 0.63, 2.63) | 1.29 | ( 0.62, 2.67) | 0.00 | (-0.01,0.02) | |
| Macroalbuminuria (>300) | 311 | 3 | 1.0 | 318 | 6 | 1.9 | 0.3302 | 1.96 | ( 0.49, 7.75) | 1.97 | ( 0.49, 7.97) | 0.01 | (-0.01,0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9249 |
| Low, moderate or high | 1477 | 13 | 0.9 | 1548 | 19 | 1.2 | 0.3508 | 1.39 | ( 0.69, 2.81) | 1.40 | ( 0.69, 2.84) | 0.00 | ( 0.00,0.01) | |
| Very high | 519 | 10 | 1.9 | 495 | 14 | 2.8 | 0.3452 | 1.47 | ( 0.66, 3.27) | 1.48 | ( 0.65, 3.37) | 0.01 | (-0.01,0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6616 |
| No | 411 | 8 | 1.9 | 410 | 9 | 2.2 | 0.8025 | 1.13 | ( 0.44, 2.89) | 1.13 | ( 0.43, 2.96) | 0.00 | (-0.02,0.02) | |
| Yes | 1590 | 16 | 1.0 | 1642 | 24 | 1.5 | 0.2418 | 1.45 | ( 0.77, 2.72) | 1.46 | ( 0.77, 2.76) | 0.00 | ( 0.00,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2404 |
| No | 282 | 5 | 1.8 | 277 | 3 | 1.1 | 0.4922 | 0.61 | ( 0.15, 2.53) | 0.61 | ( 0.14, 2.56) | -0.01 | (-0.03,0.01) | |
| Yes | 1719 | 19 | 1.1 | 1775 | 30 | 1.7 | 0.1416 | 1.53 | ( 0.86, 2.71) | 1.54 | ( 0.86, 2.74) | 0.01 | ( 0.00,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1607 |
| No | 229 | 1 | 0.4 | 250 | 6 | 2.4 | 0.0737 | 5.50 | ( 0.67, 45.31) | 5.61 | ( 0.67, 46.93) | 0.02 | ( 0.00,0.04) | |
| Yes | 1772 | 23 | 1.3 | 1802 | 27 | 1.5 | 0.6101 | 1.15 | ( 0.66, 2.01) | 1.16 | ( 0.66, 2.03) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 3 | 0.1 | 2052 | 6 | 0.3 | 0.3353 | 1.95 ( 0.49, 7.79) | 1.95 ( 0.49, 7.82) | 0.00 ( 0.00,0.00) | |
| Sex | | | | | | | | | | | |
| Male | 1065 | 3 | 0.3 | 1093 | 4 | 0.4 | | | | | |
| Female | 936 | 0 | 0 | 959 | 2 | 0.2 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 331 | 0 | 0 | 313 | 0 | 0 | | | | | |
| >=65 | 1670 | 3 | 0.2 | 1739 | 6 | 0.3 | | | | | |
| Region | | | | | | | | | | | |
| North America | 273 | 0 | 0 | 273 | 0 | 0 | | | | | |
| Latin America | 511 | 1 | 0.2 | 504 | 1 | 0.2 | | | | | |
| Europe | 865 | 2 | 0.2 | 894 | 3 | 0.3 | | | | | |
| Asia | 231 | 0 | 0 | 248 | 2 | 0.8 | | | | | |
| Other | 121 | 0 | 0 | 133 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 1045 | 2 | 0.2 | 1081 | 3 | 0.3 | | | | | |
| Non-Diabetic | 956 | 1 | 0.1 | 971 | 3 | 0.3 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 1086 | 2 | 0.2 | 1094 | 3 | 0.3 | | | | | |
| >=30 | 915 | 1 | 0.1 | 958 | 3 | 0.3 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 827 | 1 | 0.1 | 853 | 5 | 0.6 | | | | | |
| >=130 | 1174 | 2 | 0.2 | 1199 | 1 | 0.1 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 935 | 1 | 0.1 | 934 | 6 | 0.6 | | | | | |
| 75 to <85 | 657 | 0 | 0 | 703 | 0 | 0 | | | | | |
| >=85 | 409 | 2 | 0.5 | 415 | 0 | 0 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 161 | 1 | 0.6 | 148 | 1 | 0.7 | | | | | |
| 30 to <45 | 550 | 1 | 0.2 | 564 | 0 | 0 | | | | | |
| >=45 | 1289 | 1 | 0.1 | 1340 | 5 | 0.4 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 764 | 2 | 0.3 | 787 | 2 | 0.3 | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 0 | 0 | 938 | 4 | 0.4 | | | | | |
| Macroalbuminuria (>300) | 311 | 1 | 0.3 | 318 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1477 | 2 | 0.1 | 1548 | 5 | 0.3 | | | | | |
| Very high | 519 | 1 | 0.2 | 495 | 1 | 0.2 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 411 | 0 | 0 | 410 | 2 | 0.5 | | | | | |
| Yes | 1590 | 3 | 0.2 | 1642 | 4 | 0.2 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 282 | 1 | 0.4 | 277 | 0 | 0 | | | | | |
| Yes | 1719 | 2 | 0.1 | 1775 | 6 | 0.3 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 229 | 0 | 0 | 250 | 1 | 0.4 | | | | | |
| Yes | 1772 | 3 | 0.2 | 1802 | 5 | 0.3 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 26 | 1.3 | 2052 | 42 | 2.0 | 0.0640 | 1.58 | ( 0.97, 2.56) | 1.59 | ( 0.97, 2.60) | 0.01 | ( 0.00,0.02) | |
| Sex | | | | | | | | | | | | | | 0.9155 |
| Male | 1065 | 17 | 1.6 | 1093 | 28 | 2.6 | 0.1166 | 1.60 | ( 0.88, 2.91) | 1.62 | ( 0.88, 2.98) | 0.01 | ( 0.00,0.02) | |
| Female | 936 | 9 | 1.0 | 959 | 14 | 1.5 | 0.3219 | 1.52 | ( 0.66, 3.49) | 1.53 | ( 0.66, 3.54) | 0.00 | ( 0.00,0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.7140 |
| <65 | 331 | 2 | 0.6 | 313 | 4 | 1.3 | 0.3738 | 2.12 | ( 0.39, 11.47) | 2.13 | ( 0.39, 11.71) | 0.01 | (-0.01,0.02) | |
| >=65 | 1670 | 24 | 1.4 | 1739 | 38 | 2.2 | 0.1023 | 1.52 | ( 0.92, 2.52) | 1.53 | ( 0.91, 2.57) | 0.01 | ( 0.00,0.02) | |
| Region | | | | | | | | | | | | | | 0.6248 |
| North America | 273 | 8 | 2.9 | 273 | 18 | 6.6 | 0.0445 | 2.25 | (<1.00, 5.09) | 2.34 | ( 1.00, 5.47) | 0.04 | ( 0.00,0.07) | |
| Latin America | 511 | 5 | 1.0 | 504 | 9 | 1.8 | 0.2702 | 1.83 | ( 0.62, 5.41) | 1.84 | ( 0.61, 5.53) | 0.01 | (-0.01,0.02) | |
| Europe | 865 | 10 | 1.2 | 894 | 9 | 1.0 | 0.7619 | 0.87 | ( 0.36, 2.13) | 0.87 | ( 0.35, 2.15) | 0.00 | (-0.01,0.01) | |
| Asia | 231 | 0 | 0 | 248 | 1 | 0.4 | 0.5100 | 2.80 | ( 0.11, 68.27) | 2.81 | ( 0.11, 69.23) | 0.00 | (-0.01,0.02) | |
| Other | 121 | 3 | 2.5 | 133 | 5 | 3.8 | 0.5596 | 1.52 | ( 0.37, 6.21) | 1.54 | ( 0.36, 6.57) | 0.01 | (-0.03,0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0576 |
| Diabetic | 1045 | 19 | 1.8 | 1081 | 21 | 1.9 | 0.8328 | 1.07 | ( 0.58, 1.98) | 1.07 | ( 0.57, 2.00) | 0.00 | (-0.01,0.01) | |
| Non-Diabetic | 956 | 7 | 0.7 | 971 | 21 | 2.2 | 0.0087 | 2.95 | ( 1.26, 6.92) | 3.00 | ( 1.27, 7.08) | 0.01 | ( 0.00,0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0528 |
| <30 | 1086 | 7 | 0.6 | 1094 | 21 | 1.9 | 0.0082 | 2.98 | ( 1.27, 6.98) | 3.02 | ( 1.28, 7.13) | 0.01 | ( 0.00,0.02) | |
| >=30 | 915 | 19 | 2.1 | 958 | 21 | 2.2 | 0.8627 | 1.06 | ( 0.57, 1.95) | 1.06 | ( 0.56, 1.98) | 0.00 | (-0.01,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5494 |
| <130 | 827 | 13 | 1.6 | 853 | 18 | 2.1 | 0.4125 | 1.34 | ( 0.66, 2.72) | 1.35 | ( 0.66, 2.77) | 0.01 | (-0.01,0.02) | |
| >=130 | 1174 | 13 | 1.1 | 1199 | 24 | 2.0 | 0.0787 | 1.81 | ( 0.92, 3.53) | 1.82 | ( 0.92, 3.60) | 0.01 | ( 0.00,0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4334 |
| <75 | 935 | 15 | 1.6 | 934 | 22 | 2.4 | 0.2438 | 1.47 | ( 0.77, 2.81) | 1.48 | ( 0.76, 2.87) | 0.01 | (-0.01,0.02) | |
| 75 to <85 | 657 | 5 | 0.8 | 703 | 14 | 2.0 | 0.0534 | 2.62 | ( 0.95, 7.22) | 2.65 | ( 0.95, 7.40) | 0.01 | ( 0.00,0.02) | |
| >=85 | 409 | 6 | 1.5 | 415 | 6 | 1.4 | 0.9797 | 0.99 | ( 0.32, 3.03) | 0.99 | ( 0.32, 3.08) | 0.00 | (-0.02,0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5880 |
| <30 | 161 | 6 | 3.7 | 148 | 8 | 5.4 | 0.4785 | 1.45 | ( 0.52, 4.08) | 1.48 | ( 0.50, 4.36) | 0.02 | (-0.03,0.06) | |
| 30 to <45 | 550 | 8 | 1.5 | 564 | 9 | 1.6 | 0.8476 | 1.10 | ( 0.43, 2.82) | 1.10 | ( 0.42, 2.87) | 0.00 | (-0.01,0.02) | |
| >=45 | 1289 | 12 | 0.9 | 1340 | 25 | 1.9 | 0.0420 | 2.00 | ( 1.01, 3.97) | 2.02 | ( 1.01, 4.04) | 0.01 | ( 0.00,0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2326 |
| Normal (<30) | 764 | 11 | 1.4 | 787 | 12 | 1.5 | 0.8899 | 1.06 | ( 0.47, 2.39) | 1.06 | ( 0.46, 2.42) | 0.00 | (-0.01,0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 10 | 1.1 | 938 | 25 | 2.7 | 0.0122 | 2.45 | ( 1.19, 5.08) | 2.49 | ( 1.19, 5.22) | 0.02 | ( 0.00,0.03) | |
| Macroalbuminuria (>300) | 311 | 5 | 1.6 | 318 | 5 | 1.6 | 0.9717 | 0.98 | ( 0.29, 3.34) | 0.98 | ( 0.28, 3.41) | 0.00 | (-0.02,0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8768 |
| Low, moderate or high | 1477 | 16 | 1.1 | 1548 | 26 | 1.7 | 0.1612 | 1.55 | ( 0.84, 2.88) | 1.56 | ( 0.83, 2.92) | 0.01 | ( 0.00,0.01) | |
| Very high | 519 | 10 | 1.9 | 495 | 16 | 3.2 | 0.1886 | 1.68 | ( 0.77, 3.66) | 1.70 | ( 0.76, 3.78) | 0.01 | (-0.01,0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9356 |
| No | 411 | 8 | 1.9 | 410 | 13 | 3.2 | 0.2666 | 1.63 | ( 0.68, 3.89) | 1.65 | ( 0.68, 4.02) | 0.01 | (-0.01,0.03) | |
| Yes | 1590 | 18 | 1.1 | 1642 | 29 | 1.8 | 0.1322 | 1.56 | ( 0.87, 2.80) | 1.57 | ( 0.87, 2.84) | 0.01 | ( 0.00,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6432 |
| No | 282 | 4 | 1.4 | 277 | 8 | 2.9 | 0.2307 | 2.04 | ( 0.62, 6.68) | 2.07 | ( 0.62, 6.94) | 0.01 | (-0.01,0.04) | |
| Yes | 1719 | 22 | 1.3 | 1775 | 34 | 1.9 | 0.1347 | 1.50 | ( 0.88, 2.55) | 1.51 | ( 0.88, 2.59) | 0.01 | ( 0.00,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6272 |
| No | 229 | 3 | 1.3 | 250 | 7 | 2.8 | 0.2546 | 2.14 | ( 0.56, 8.17) | 2.17 | ( 0.55, 8.49) | 0.01 | (-0.01,0.04) | |
| Yes | 1772 | 23 | 1.3 | 1802 | 35 | 1.9 | 0.1275 | 1.50 | ( 0.89, 2.52) | 1.51 | ( 0.89, 2.56) | 0.01 | ( 0.00,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 20 | 1.0 | 2052 | 38 | 1.9 | 0.0224 | 1.85 | ( 1.08, 3.17) | 1.87 | ( 1.08, 3.22) | 0.01 | ( 0.00,0.02) | |
| Sex | | | | | | | | | | | | | | 0.6363 |
| Male | 1065 | 13 | 1.2 | 1093 | 27 | 2.5 | 0.0314 | 2.02 | ( 1.05, 3.90) | 2.05 | ( 1.05, 3.99) | 0.01 | ( 0.00,0.02) | |
| Female | 936 | 7 | 0.7 | 959 | 11 | 1.1 | 0.3704 | 1.53 | ( 0.60, 3.94) | 1.54 | ( 0.59, 3.99) | 0.00 | ( 0.00,0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.8660 |
| <65 | 331 | 2 | 0.6 | 313 | 4 | 1.3 | 0.3738 | 2.12 | ( 0.39, 11.47) | 2.13 | ( 0.39, 11.71) | 0.01 | (-0.01,0.02) | |
| >=65 | 1670 | 18 | 1.1 | 1739 | 34 | 2.0 | 0.0367 | 1.81 | ( 1.03, 3.20) | 1.83 | ( 1.03, 3.25) | 0.01 | ( 0.00,0.02) | |
| Region | | | | | | | | | | | | | | 0.7340 |
| North America | 273 | 7 | 2.6 | 273 | 17 | 6.2 | 0.0368 | 2.43 | ( 1.02, 5.76) | 2.52 | ( 1.03, 6.19) | 0.04 | ( 0.00,0.07) | |
| Latin America | 511 | 4 | 0.8 | 504 | 8 | 1.6 | 0.2358 | 2.03 | ( 0.61, 6.69) | 2.04 | ( 0.61, 6.83) | 0.01 | (-0.01,0.02) | |
| Europe | 865 | 7 | 0.8 | 894 | 7 | 0.8 | 0.9506 | 0.97 | ( 0.34, 2.75) | 0.97 | ( 0.34, 2.77) | 0.00 | (-0.01,0.01) | |
| Asia | 231 | 0 | 0 | 248 | 1 | 0.4 | 0.5100 | 2.80 | ( 0.11, 68.27) | 2.81 | ( 0.11, 69.23) | 0.00 | (-0.01,0.02) | |
| Other | 121 | 2 | 1.7 | 133 | 5 | 3.8 | 0.3057 | 2.27 | ( 0.45, 11.51) | 2.32 | ( 0.44, 12.21) | 0.02 | (-0.02,0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3480 |
| Diabetic | 1045 | 13 | 1.2 | 1081 | 20 | 1.9 | 0.2584 | 1.49 | ( 0.74, 2.97) | 1.50 | ( 0.74, 3.02) | 0.01 | ( 0.00,0.02) | |
| Non-Diabetic | 956 | 7 | 0.7 | 971 | 18 | 1.9 | 0.0296 | 2.53 | ( 1.06, 6.03) | 2.56 | ( 1.06, 6.16) | 0.01 | ( 0.00,0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4317 |
| <30 | 1086 | 7 | 0.6 | 1094 | 17 | 1.6 | 0.0419 | 2.41 | (>1.00, 5.79) | 2.43 | ( 1.00, 5.89) | 0.01 | ( 0.00,0.02) | |
| >=30 | 915 | 13 | 1.4 | 958 | 21 | 2.2 | 0.2114 | 1.54 | ( 0.78, 3.06) | 1.56 | ( 0.77, 3.12) | 0.01 | ( 0.00,0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9703 |
| <130 | 827 | 9 | 1.1 | 853 | 17 | 2.0 | 0.1331 | 1.83 | ( 0.82, 4.08) | 1.85 | ( 0.82, 4.17) | 0.01 | ( 0.00,0.02) | |
| >=130 | 1174 | 11 | 0.9 | 1199 | 21 | 1.8 | 0.0855 | 1.87 | ( 0.91, 3.86) | 1.88 | ( 0.90, 3.93) | 0.01 | ( 0.00,0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6438 |
| <75 | 935 | 11 | 1.2 | 934 | 21 | 2.2 | 0.0741 | 1.91 | ( 0.93, 3.94) | 1.93 | ( 0.93, 4.03) | 0.01 | ( 0.00,0.02) | |
| 75 to <85 | 657 | 4 | 0.6 | 703 | 11 | 1.6 | 0.0917 | 2.57 | ( 0.82, 8.03) | 2.60 | ( 0.82, 8.19) | 0.01 | ( 0.00,0.02) | |
| >=85 | 409 | 5 | 1.2 | 415 | 6 | 1.4 | 0.7801 | 1.18 | ( 0.36, 3.84) | 1.19 | ( 0.36, 3.91) | 0.00 | (-0.01,0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.7492 |
| <30 | 161 | 5 | 3.1 | 148 | 6 | 4.1 | 0.6531 | 1.31 | ( 0.41, | 4.19) | 1.32 | ( 0.39, | 4.41) | 0.01 | (-0.03,0.05) | |
| 30 to <45 | 550 | 5 | 0.9 | 564 | 9 | 1.6 | 0.3037 | 1.76 | ( 0.59, | 5.20) | 1.77 | ( 0.59, | 5.31) | 0.01 | (-0.01,0.02) | |
| >=45 | 1289 | 10 | 0.8 | 1340 | 23 | 1.7 | 0.0303 | 2.21 | ( 1.06, | 4.63) | 2.23 | ( 1.06, | 4.71) | 0.01 | ( 0.00,0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.7405 |
| Normal (<30) | 764 | 8 | 1.0 | 787 | 12 | 1.5 | 0.4045 | 1.46 | ( 0.60, | 3.54) | 1.46 | ( 0.59, | 3.60) | 0.00 | (-0.01,0.02) | |
| Microalbuminuria (30 to <=300) | 921 | 9 | 1.0 | 938 | 21 | 2.2 | 0.0309 | 2.29 | ( 1.05, | 4.98) | 2.32 | ( 1.06, | 5.09) | 0.01 | ( 0.00,0.02) | |
| Macroalbuminuria (>300) | 311 | 3 | 1.0 | 318 | 5 | 1.6 | 0.4965 | 1.63 | ( 0.39, | 6.76) | 1.64 | ( 0.39, | 6.92) | 0.01 | (-0.01,0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.7607 |
| Low, moderate or high | 1477 | 13 | 0.9 | 1548 | 24 | 1.6 | 0.0937 | 1.76 | ( 0.90, | 3.45) | 1.77 | ( 0.90, | 3.50) | 0.01 | ( 0.00,0.01) | |
| Very high | 519 | 7 | 1.3 | 495 | 14 | 2.8 | 0.0982 | 2.10 | ( 0.85, | 5.15) | 2.13 | ( 0.85, | 5.32) | 0.01 | ( 0.00,0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | | | 0.6391 |
| No | 411 | 6 | 1.5 | 410 | 9 | 2.2 | 0.4316 | 1.50 | ( 0.54, | 4.19) | 1.51 | ( 0.53, | 4.30) | 0.01 | (-0.01,0.03) | |
| Yes | 1590 | 14 | 0.9 | 1642 | 29 | 1.8 | 0.0280 | 2.01 | ( 1.06, | 3.78) | 2.02 | ( 1.07, | 3.84) | 0.01 | ( 0.00,0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.8663 |
| No | 282 | 4 | 1.4 | 277 | 8 | 2.9 | 0.2307 | 2.04 | ( 0.62, | 6.68) | 2.07 | ( 0.62, | 6.94) | 0.01 | (-0.01,0.04) | |
| Yes | 1719 | 16 | 0.9 | 1775 | 30 | 1.7 | 0.0490 | 1.82 | ( 0.99, | 3.32) | 1.83 | ( 0.99, | 3.37) | 0.01 | ( 0.00,0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.9892 |
| No | 229 | 3 | 1.3 | 250 | 6 | 2.4 | 0.3802 | 1.83 | ( 0.46, | 7.24) | 1.85 | ( 0.46, | 7.49) | 0.01 | (-0.01,0.03) | |
| Yes | 1772 | 17 | 1.0 | 1802 | 32 | 1.8 | 0.0359 | 1.85 | ( 1.03, | 3.32) | 1.87 | ( 1.03, | 3.37) | 0.01 | ( 0.00,0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 95 | 4.7 | 2052 | 72 | 3.5 | 0.0473 | 0.74 | ( 0.55, <1.00) | 0.73 | ( 0.53, 1.00) | -0.01 | (-0.02,0.00) | |
| Sex | | | | | | | | | | | | | | 0.5039 |
| Male | 1065 | 51 | 4.8 | 1093 | 35 | 3.2 | 0.0596 | 0.67 | ( 0.44, 1.02) | 0.66 | ( 0.42, 1.02) | -0.02 | (-0.03,0.00) | |
| Female | 936 | 44 | 4.7 | 959 | 37 | 3.9 | 0.3646 | 0.82 | ( 0.54, 1.26) | 0.81 | ( 0.52, 1.27) | -0.01 | (-0.03,0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3836 |
| <65 | 331 | 15 | 4.5 | 313 | 14 | 4.5 | 0.9713 | 0.99 | ( 0.48, 2.01) | 0.99 | ( 0.47, 2.08) | 0.00 | (-0.03,0.03) | |
| >=65 | 1670 | 80 | 4.8 | 1739 | 58 | 3.3 | 0.0312 | 0.70 | ( 0.50, 0.97) | 0.69 | ( 0.49, 0.97) | -0.01 | (-0.03,0.00) | |
| Region | | | | | | | | | | | | | | 0.4220 |
| North America | 273 | 22 | 8.1 | 273 | 17 | 6.2 | 0.4061 | 0.77 | ( 0.42, 1.42) | 0.76 | ( 0.39, 1.46) | -0.02 | (-0.06,0.02) | |
| Latin America | 511 | 26 | 5.1 | 504 | 28 | 5.6 | 0.7400 | 1.09 | ( 0.65, 1.84) | 1.10 | ( 0.63, 1.90) | 0.00 | (-0.02,0.03) | |
| Europe | 865 | 31 | 3.6 | 894 | 17 | 1.9 | 0.0304 | 0.53 | ( 0.30, 0.95) | 0.52 | ( 0.29, 0.95) | -0.02 | (-0.03,0.00) | |
| Asia | 231 | 9 | 3.9 | 248 | 5 | 2.0 | 0.2223 | 0.52 | ( 0.18, 1.52) | 0.51 | ( 0.17, 1.54) | -0.02 | (-0.05,0.01) | |
| Other | 121 | 7 | 5.8 | 133 | 5 | 3.8 | 0.4473 | 0.65 | ( 0.21, 1.99) | 0.64 | ( 0.20, 2.06) | -0.02 | (-0.07,0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3715 |
| Diabetic | 1045 | 58 | 5.6 | 1081 | 49 | 4.5 | 0.2834 | 0.82 | ( 0.56, 1.18) | 0.81 | ( 0.55, 1.19) | -0.01 | (-0.03,0.01) | |
| Non-Diabetic | 956 | 37 | 3.9 | 971 | 23 | 2.4 | 0.0578 | 0.61 | ( 0.37, 1.02) | 0.60 | ( 0.36, 1.02) | -0.02 | (-0.03,0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9798 |
| <30 | 1086 | 38 | 3.5 | 1094 | 28 | 2.6 | 0.2005 | 0.73 | ( 0.45, 1.18) | 0.72 | ( 0.44, 1.19) | -0.01 | (-0.02,0.00) | |
| >=30 | 915 | 57 | 6.2 | 958 | 44 | 4.6 | 0.1170 | 0.74 | ( 0.50, 1.08) | 0.72 | ( 0.48, 1.09) | -0.02 | (-0.04,0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9686 |
| <130 | 827 | 37 | 4.5 | 853 | 28 | 3.3 | 0.2055 | 0.73 | ( 0.45, 1.19) | 0.72 | ( 0.44, 1.20) | -0.01 | (-0.03,0.01) | |
| >=130 | 1174 | 58 | 4.9 | 1199 | 44 | 3.7 | 0.1270 | 0.74 | ( 0.51, 1.09) | 0.73 | ( 0.49, 1.09) | -0.01 | (-0.03,0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5921 |
| <75 | 935 | 49 | 5.2 | 934 | 38 | 4.1 | 0.2291 | 0.78 | ( 0.51, 1.17) | 0.77 | ( 0.50, 1.18) | -0.01 | (-0.03,0.01) | |
| 75 to <85 | 657 | 30 | 4.6 | 703 | 19 | 2.7 | 0.0654 | 0.59 | ( 0.34, 1.04) | 0.58 | ( 0.32, 1.04) | -0.02 | (-0.04,0.00) | |
| >=85 | 409 | 16 | 3.9 | 415 | 15 | 3.6 | 0.8224 | 0.92 | ( 0.46, 1.84) | 0.92 | ( 0.45, 1.89) | 0.00 | (-0.03,0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5296 |
| <30 | 161 | 27 | 16.8 | 148 | 19 | 12.8 | 0.3320 | 0.77 | ( 0.44, 1.32) | 0.73 | ( 0.39, 1.38) | -0.04 | (-0.12,0.04) | |
| 30 to <45 | 550 | 28 | 5.1 | 564 | 27 | 4.8 | 0.8151 | 0.94 | ( 0.56, 1.57) | 0.94 | ( 0.55, 1.61) | 0.00 | (-0.03,0.02) | |
| >=45 | 1289 | 40 | 3.1 | 1340 | 26 | 1.9 | 0.0567 | 0.63 | ( 0.38, 1.02) | 0.62 | ( 0.37, 1.02) | -0.01 | (-0.02,0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4082 |
| Normal (<30) | 764 | 28 | 3.7 | 787 | 22 | 2.8 | 0.3324 | 0.76 | ( 0.44, 1.32) | 0.76 | ( 0.43, 1.33) | -0.01 | (-0.03,0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 39 | 4.2 | 938 | 23 | 2.5 | 0.0323 | 0.58 | ( 0.35, 0.96) | 0.57 | ( 0.34, 0.96) | -0.02 | (-0.03,0.00) | |
| Macroalbuminuria (>300) | 311 | 28 | 9.0 | 318 | 27 | 8.5 | 0.8200 | 0.94 | ( 0.57, 1.56) | 0.94 | ( 0.54, 1.63) | -0.01 | (-0.05,0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.6400 |
| Low, moderate or high | 1477 | 46 | 3.1 | 1548 | 34 | 2.2 | 0.1157 | 0.71 | ( 0.46, 1.09) | 0.70 | ( 0.45, 1.09) | -0.01 | (-0.02,0.00) | |
| Very high | 519 | 49 | 9.4 | 495 | 38 | 7.7 | 0.3160 | 0.81 | ( 0.54, 1.22) | 0.80 | ( 0.51, 1.24) | -0.02 | (-0.05,0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4568 |
| No | 411 | 25 | 6.1 | 410 | 15 | 3.7 | 0.1067 | 0.60 | ( 0.32, 1.12) | 0.59 | ( 0.30, 1.13) | -0.02 | (-0.05,0.01) | |
| Yes | 1590 | 70 | 4.4 | 1642 | 57 | 3.5 | 0.1732 | 0.79 | ( 0.56, 1.11) | 0.78 | ( 0.55, 1.12) | -0.01 | (-0.02,0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9290 |
| No | 282 | 17 | 6.0 | 277 | 12 | 4.3 | 0.3659 | 0.72 | ( 0.35, 1.48) | 0.71 | ( 0.33, 1.51) | -0.02 | (-0.05,0.02) | |
| Yes | 1719 | 78 | 4.5 | 1775 | 60 | 3.4 | 0.0791 | 0.74 | ( 0.54, 1.04) | 0.74 | ( 0.52, 1.04) | -0.01 | (-0.02,0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9839 |
| No | 229 | 5 | 2.2 | 250 | 4 | 1.6 | 0.6385 | 0.73 | ( 0.20, 2.70) | 0.73 | ( 0.19, 2.75) | -0.01 | (-0.03,0.02) | |
| Yes | 1772 | 90 | 5.1 | 1802 | 68 | 3.8 | 0.0577 | 0.74 | ( 0.55, 1.01) | 0.73 | ( 0.53, 1.01) | -0.01 | (-0.03,0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 5 | 0.2 | 2052 | 2 | 0.1 | 0.2427 | 0.39 | ( 0.08, 2.01) | 0.39 | ( 0.08, 2.01) | 0.00 ( 0.00,0.00) | |
| Sex | | | | | | | | | | | | | |
| Male | 1065 | 2 | 0.2 | 1093 | 2 | 0.2 | | | | | | | |
| Female | 936 | 3 | 0.3 | 959 | 0 | 0 | | | | | | | |
| Age [years] | | | | | | | | | | | | | |
| <65 | 331 | 0 | 0 | 313 | 0 | 0 | | | | | | | |
| >=65 | 1670 | 5 | 0.3 | 1739 | 2 | 0.1 | | | | | | | |
| Region | | | | | | | | | | | | | |
| North America | 273 | 3 | 1.1 | 273 | 2 | 0.7 | | | | | | | |
| Latin America | 511 | 0 | 0 | 504 | 0 | 0 | | | | | | | |
| Europe | 865 | 1 | 0.1 | 894 | 0 | 0 | | | | | | | |
| Asia | 231 | 0 | 0 | 248 | 0 | 0 | | | | | | | |
| Other | 121 | 1 | 0.8 | 133 | 0 | 0 | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | |
| Diabetic | 1045 | 3 | 0.3 | 1081 | 1 | 0.1 | | | | | | | |
| Non-Diabetic | 956 | 2 | 0.2 | 971 | 1 | 0.1 | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | |
| <30 | 1086 | 3 | 0.3 | 1094 | 2 | 0.2 | | | | | | | |
| >=30 | 915 | 2 | 0.2 | 958 | 0 | 0 | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | |
| <130 | 827 | 2 | 0.2 | 853 | 1 | 0.1 | | | | | | | |
| >=130 | 1174 | 3 | 0.3 | 1199 | 1 | 0.1 | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | |
| <75 | 935 | 4 | 0.4 | 934 | 2 | 0.2 | | | | | | | |
| 75 to <85 | 657 | 1 | 0.2 | 703 | 0 | 0 | | | | | | | |
| >=85 | 409 | 0 | 0 | 415 | 0 | 0 | | | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 161 | 1 | 0.6 | 148 | 1 | 0.7 | | | | | |
| 30 to <45 | 550 | 1 | 0.2 | 564 | 0 | 0 | | | | | |
| >=45 | 1289 | 3 | 0.2 | 1340 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 764 | 4 | 0.5 | 787 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 1 | 0.1 | 938 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 311 | 0 | 0 | 318 | 2 | 0.6 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1477 | 4 | 0.3 | 1548 | 0 | 0 | | | | | |
| Very high | 519 | 1 | 0.2 | 495 | 2 | 0.4 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 411 | 2 | 0.5 | 410 | 1 | 0.2 | | | | | |
| Yes | 1590 | 3 | 0.2 | 1642 | 1 | 0.1 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 282 | 0 | 0 | 277 | 1 | 0.4 | | | | | |
| Yes | 1719 | 5 | 0.3 | 1775 | 1 | 0.1 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 229 | 0 | 0 | 250 | 0 | 0 | | | | | |
| Yes | 1772 | 5 | 0.3 | 1802 | 2 | 0.1 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 4 | 0.2 | 2052 | 5 | 0.2 | 0.7673 | 1.22 | ( 0.33, 4.53) | 1.22 | ( 0.33, 4.55) | 0.00 ( 0.00,0.00) | |
| Sex | | | | | | | | | | | | | |
| Male | 1065 | 4 | 0.4 | 1093 | 2 | 0.2 | | | | | | | |
| Female | 936 | 0 | 0 | 959 | 3 | 0.3 | | | | | | | |
| Age [years] | | | | | | | | | | | | | |
| <65 | 331 | 1 | 0.3 | 313 | 0 | 0 | | | | | | | |
| >=65 | 1670 | 3 | 0.2 | 1739 | 5 | 0.3 | | | | | | | |
| Region | | | | | | | | | | | | | |
| North America | 273 | 0 | 0 | 273 | 1 | 0.4 | | | | | | | |
| Latin America | 511 | 2 | 0.4 | 504 | 0 | 0 | | | | | | | |
| Europe | 865 | 1 | 0.1 | 894 | 2 | 0.2 | | | | | | | |
| Asia | 231 | 0 | 0 | 248 | 1 | 0.4 | | | | | | | |
| Other | 121 | 1 | 0.8 | 133 | 1 | 0.8 | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | |
| Diabetic | 1045 | 4 | 0.4 | 1081 | 4 | 0.4 | | | | | | | |
| Non-Diabetic | 956 | 0 | 0 | 971 | 1 | 0.1 | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | |
| <30 | 1086 | 2 | 0.2 | 1094 | 1 | 0.1 | | | | | | | |
| >=30 | 915 | 2 | 0.2 | 958 | 4 | 0.4 | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | |
| <130 | 827 | 2 | 0.2 | 853 | 2 | 0.2 | | | | | | | |
| >=130 | 1174 | 2 | 0.2 | 1199 | 3 | 0.3 | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | |
| <75 | 935 | 2 | 0.2 | 934 | 1 | 0.1 | | | | | | | |
| 75 to <85 | 657 | 2 | 0.3 | 703 | 3 | 0.4 | | | | | | | |
| >=85 | 409 | 0 | 0 | 415 | 1 | 0.2 | | | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 161 | 0 | 0 | 148 | 2 | 1.4 | | | | | |
| 30 to <45 | 550 | 1 | 0.2 | 564 | 2 | 0.4 | | | | | |
| >=45 | 1289 | 3 | 0.2 | 1340 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 764 | 0 | 0 | 787 | 3 | 0.4 | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 3 | 0.3 | 938 | 2 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 311 | 1 | 0.3 | 318 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1477 | 2 | 0.1 | 1548 | 3 | 0.2 | | | | | |
| Very high | 519 | 2 | 0.4 | 495 | 2 | 0.4 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 411 | 0 | 0 | 410 | 3 | 0.7 | | | | | |
| Yes | 1590 | 4 | 0.3 | 1642 | 2 | 0.1 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 282 | 0 | 0 | 277 | 1 | 0.4 | | | | | |
| Yes | 1719 | 4 | 0.2 | 1775 | 4 | 0.2 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 229 | 0 | 0 | 250 | 0 | 0 | | | | | |
| Yes | 1772 | 4 | 0.2 | 1802 | 5 | 0.3 | | | | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 15 | 0.7 | 2052 | 8 | 0.4 | 0.1274 | 0.52 | ( 0.22, 1.22) | 0.52 | ( 0.22, 1.22) | 0.00 | (-0.01,0.00) | |
| Sex | | | | | | | | | | | | | | 0.6807 |
| Male | 1065 | 10 | 0.9 | 1093 | 6 | 0.5 | 0.2910 | 0.58 | ( 0.21, 1.60) | 0.58 | ( 0.21, 1.61) | 0.00 | (-0.01,0.00) | |
| Female | 936 | 5 | 0.5 | 959 | 2 | 0.2 | 0.2427 | 0.39 | ( 0.08, 2.01) | 0.39 | ( 0.08, 2.01) | 0.00 | (-0.01,0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.7523 |
| <65 | 331 | 5 | 1.5 | 313 | 2 | 0.6 | 0.2863 | 0.42 | ( 0.08, 2.16) | 0.42 | ( 0.08, 2.18) | -0.01 | (-0.02,0.01) | |
| >=65 | 1670 | 10 | 0.6 | 1739 | 6 | 0.3 | 0.2785 | 0.58 | ( 0.21, 1.58) | 0.57 | ( 0.21, 1.58) | 0.00 | (-0.01,0.00) | |
| Region | | | | | | | | | | | | | | |
| North America | 273 | 4 | 1.5 | 273 | 1 | 0.4 | | | | | | | | |
| Latin America | 511 | 6 | 1.2 | 504 | 2 | 0.4 | | | | | | | | |
| Europe | 865 | 2 | 0.2 | 894 | 0 | 0 | | | | | | | | |
| Asia | 231 | 1 | 0.4 | 248 | 1 | 0.4 | | | | | | | | |
| Other | 121 | 2 | 1.7 | 133 | 4 | 3.0 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5779 |
| Diabetic | 1045 | 11 | 1.1 | 1081 | 5 | 0.5 | 0.1155 | 0.44 | ( 0.15, 1.26) | 0.44 | ( 0.15, 1.26) | -0.01 | (-0.01,0.00) | |
| Non-Diabetic | 956 | 4 | 0.4 | 971 | 3 | 0.3 | 0.6897 | 0.74 | ( 0.17, 3.29) | 0.74 | ( 0.16, 3.30) | 0.00 | (-0.01,0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0943 |
| <30 | 1086 | 4 | 0.4 | 1094 | 5 | 0.5 | 0.7467 | 1.24 | ( 0.33, 4.61) | 1.24 | ( 0.33, 4.64) | 0.00 | ( 0.00,0.01) | |
| >=30 | 915 | 11 | 1.2 | 958 | 3 | 0.3 | 0.0256 | 0.26 | ( 0.07, 0.93) | 0.26 | ( 0.07, 0.93) | -0.01 | (-0.02,0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0663 |
| <130 | 827 | 10 | 1.2 | 853 | 2 | 0.2 | 0.0177 | 0.19 | ( 0.04, 0.88) | 0.19 | ( 0.04, 0.88) | -0.01 | (-0.02,0.00) | |
| >=130 | 1174 | 5 | 0.4 | 1199 | 6 | 0.5 | 0.7893 | 1.17 | ( 0.36, 3.84) | 1.18 | ( 0.36, 3.86) | 0.00 | ( 0.00,0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3875 |
| <75 | 935 | 7 | 0.7 | 934 | 5 | 0.5 | 0.5637 | 0.72 | ( 0.23, 2.24) | 0.71 | ( 0.23, 2.26) | 0.00 | (-0.01,0.01) | |
| 75 to <85 | 657 | 6 | 0.9 | 703 | 1 | 0.1 | 0.0471 | 0.16 | ( 0.02, 1.29) | 0.15 | ( 0.02, 1.29) | -0.01 | (-0.02,0.00) | |
| >=85 | 409 | 2 | 0.5 | 415 | 2 | 0.5 | 0.9884 | 0.99 | ( 0.14, 6.96) | 0.99 | ( 0.14, 7.03) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7898 |
| <30 | 161 | 4 | 2.5 | 148 | 1 | 0.7 | 0.2081 | 0.27 | ( 0.03, 2.41) | 0.27 | ( 0.03, 2.42) | -0.02 | (-0.05,0.01) | |
| 30 to <45 | 550 | 6 | 1.1 | 564 | 4 | 0.7 | 0.4995 | 0.65 | ( 0.18, 2.29) | 0.65 | ( 0.18, 2.31) | 0.00 | (-0.01,0.01) | |
| >=45 | 1289 | 5 | 0.4 | 1340 | 3 | 0.2 | 0.4453 | 0.58 | ( 0.14, 2.41) | 0.58 | ( 0.14, 2.42) | 0.00 | (-0.01,0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | |
| Normal (<30) | 764 | 6 | 0.8 | 787 | 3 | 0.4 | | | | | | | | |
| Microalbuminuria (30 to <=300) | 921 | 3 | 0.3 | 938 | 2 | 0.2 | | | | | | | | |
| Macroalbuminuria (>300) | 311 | 6 | 1.9 | 318 | 3 | 0.9 | | | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7942 |
| Low, moderate or high | 1477 | 8 | 0.5 | 1548 | 4 | 0.3 | 0.2154 | 0.48 | ( 0.14, 1.58) | 0.48 | ( 0.14, 1.58) | 0.00 | (-0.01,0.00) | |
| Very high | 519 | 7 | 1.3 | 495 | 4 | 0.8 | 0.4061 | 0.60 | ( 0.18, 2.03) | 0.60 | ( 0.17, 2.05) | -0.01 | (-0.02,0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7562 |
| No | 411 | 3 | 0.7 | 410 | 2 | 0.5 | 0.6557 | 0.67 | ( 0.11, 3.98) | 0.67 | ( 0.11, 4.01) | 0.00 | (-0.01,0.01) | |
| Yes | 1590 | 12 | 0.8 | 1642 | 6 | 0.4 | 0.1371 | 0.48 | ( 0.18, 1.29) | 0.48 | ( 0.18, 1.29) | 0.00 | (-0.01,0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1119 |
| No | 282 | 0 | 0 | 277 | 2 | 0.7 | 0.2407 | 5.09 | ( 0.25,105.54) | 5.13 | ( 0.25,107.28) | 0.01 | ( 0.00,0.02) | |
| Yes | 1719 | 15 | 0.9 | 1775 | 6 | 0.3 | 0.0410 | 0.39 | ( 0.15, <1.00) | 0.39 | ( 0.15, 1.00) | -0.01 | (-0.01,0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1296 |
| No | 229 | 0 | 0 | 250 | 2 | 0.8 | 0.2786 | 4.58 | ( 0.22, 94.93) | 4.62 | ( 0.22, 96.69) | 0.01 | (-0.01,0.02) | |
| Yes | 1772 | 15 | 0.8 | 1802 | 6 | 0.3 | 0.0446 | 0.39 | ( 0.15, 1.01) | 0.39 | ( 0.15, 1.01) | -0.01 | (-0.01,0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.2.2.4**

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 903 | 45.1 | 2052 | 903 | 44.0 | 0.4726 | 0.98 ( 0.91, 1.04) | 0.96 ( 0.84, 1.08) | -0.01 (-0.04, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 873 | 43.6 | 2052 | 803 | 39.1 | 0.0037 | 0.90 | ( 0.83, 0.97) | 0.83 | ( 0.73, 0.94) | -0.04 | (-0.08,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.2131 |
| Male | 1065 | 482 | 45.3 | 1093 | 425 | 38.9 | 0.0027 | 0.86 | ( 0.78, 0.95) | 0.77 | ( 0.65, 0.91) | -0.06 | (-0.11,-0.02) | |
| Female | 936 | 391 | 41.8 | 959 | 378 | 39.4 | 0.2961 | 0.94 | ( 0.85, 1.05) | 0.91 | ( 0.75, 1.09) | -0.02 | (-0.07, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.0924 |
| <65 | 331 | 121 | 36.6 | 313 | 120 | 38.3 | 0.6403 | 1.05 | ( 0.86, 1.28) | 1.08 | ( 0.78, 1.49) | 0.02 | (-0.06, 0.09) | |
| >=65 | 1670 | 752 | 45.0 | 1739 | 683 | 39.3 | 0.0007 | 0.87 | ( 0.81, 0.94) | 0.79 | ( 0.69, 0.90) | -0.06 | (-0.09,-0.02) | |
| Region | | | | | | | | | | | | | | 0.5069 |
| North America | 273 | 148 | 54.2 | 273 | 141 | 51.6 | 0.5484 | 0.95 | ( 0.81, 1.12) | 0.90 | ( 0.64, 1.26) | -0.03 | (-0.11, 0.06) | |
| Latin America | 511 | 208 | 40.7 | 504 | 180 | 35.7 | 0.1019 | 0.88 | ( 0.75, 1.03) | 0.81 | ( 0.63, 1.04) | -0.05 | (-0.11, 0.01) | |
| Europe | 865 | 369 | 42.7 | 894 | 334 | 37.4 | 0.0233 | 0.88 | ( 0.78, 0.98) | 0.80 | ( 0.66, 0.97) | -0.05 | (-0.10,-0.01) | |
| Asia | 231 | 94 | 40.7 | 248 | 103 | 41.5 | 0.8520 | 1.02 | ( 0.82, 1.26) | 1.04 | ( 0.72, 1.49) | 0.01 | (-0.08, 0.10) | |
| Other | 121 | 54 | 44.6 | 133 | 45 | 33.8 | 0.0781 | 0.76 | ( 0.56, 1.03) | 0.63 | ( 0.38, 1.05) | -0.11 | (-0.23, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2286 |
| Diabetic | 1045 | 481 | 46.0 | 1081 | 428 | 39.6 | 0.0027 | 0.86 | ( 0.78, 0.95) | 0.77 | ( 0.65, 0.91) | -0.06 | (-0.11,-0.02) | |
| Non-Diabetic | 956 | 392 | 41.0 | 971 | 375 | 38.6 | 0.2850 | 0.94 | ( 0.84, 1.05) | 0.91 | ( 0.75, 1.09) | -0.02 | (-0.07, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7207 |
| <30 | 1086 | 486 | 44.8 | 1094 | 434 | 39.7 | 0.0163 | 0.89 | ( 0.80, 0.98) | 0.81 | ( 0.68, 0.96) | -0.05 | (-0.09,-0.01) | |
| >=30 | 915 | 387 | 42.3 | 958 | 369 | 38.5 | 0.0958 | 0.91 | ( 0.82, 1.02) | 0.85 | ( 0.71, 1.03) | -0.04 | (-0.08, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5774 |
| <130 | 827 | 377 | 45.6 | 853 | 357 | 41.9 | 0.1229 | 0.92 | ( 0.82, 1.02) | 0.86 | ( 0.71, 1.04) | -0.04 | (-0.08, 0.01) | |
| >=130 | 1174 | 496 | 42.2 | 1199 | 446 | 37.2 | 0.0119 | 0.88 | ( 0.80, 0.97) | 0.81 | ( 0.69, 0.95) | -0.05 | (-0.09,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0632 |
| <75 | 935 | 417 | 44.6 | 934 | 405 | 43.4 | 0.5901 | 0.97 | ( 0.88, 1.08) | 0.95 | ( 0.79, 1.14) | -0.01 | (-0.06, 0.03) | |
| 75 to <85 | 657 | 288 | 43.8 | 703 | 245 | 34.9 | 0.0007 | 0.80 | ( 0.70, 0.91) | 0.69 | ( 0.55, 0.85) | -0.09 | (-0.14,-0.04) | |
| >=85 | 409 | 168 | 41.1 | 415 | 153 | 36.9 | 0.2155 | 0.90 | ( 0.76, 1.07) | 0.84 | ( 0.63, 1.11) | -0.04 | (-0.11, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3755 |
| <30 | 161 | 83 | 51.6 | 148 | 79 | 53.4 | 0.7482 | 1.04 | ( 0.84, 1.28) | 1.08 | ( 0.69, 1.68) | 0.02 | (-0.09, 0.13) | |
| 30 to <45 | 550 | 261 | 47.5 | 564 | 242 | 42.9 | 0.1274 | 0.90 | ( 0.79, 1.03) | 0.83 | ( 0.66, 1.05) | -0.05 | (-0.10, 0.01) | |
| >=45 | 1289 | 529 | 41.0 | 1340 | 482 | 36.0 | 0.0076 | 0.88 | ( 0.80, 0.97) | 0.81 | ( 0.69, 0.94) | -0.05 | (-0.09,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7253 |
| Normal (<30) | 764 | 323 | 42.3 | 787 | 295 | 37.5 | 0.0539 | 0.89 | ( 0.78, >1.00) | 0.82 | ( 0.67, 1.00) | -0.05 | (-0.10, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 398 | 43.2 | 938 | 375 | 40.0 | 0.1571 | 0.93 | ( 0.83, 1.03) | 0.88 | ( 0.73, 1.05) | -0.03 | (-0.08, 0.01) | |
| Macroalbuminuria (>300) | 311 | 151 | 48.6 | 318 | 132 | 41.5 | 0.0758 | 0.85 | ( 0.72, 1.02) | 0.75 | ( 0.55, 1.03) | -0.07 | (-0.15, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8461 |
| Low, moderate or high | 1477 | 611 | 41.4 | 1548 | 575 | 37.1 | 0.0174 | 0.90 | ( 0.82, 0.98) | 0.84 | ( 0.72, 0.97) | -0.04 | (-0.08,-0.01) | |
| Very high | 519 | 261 | 50.3 | 495 | 227 | 45.9 | 0.1581 | 0.91 | ( 0.80, 1.04) | 0.84 | ( 0.65, 1.07) | -0.04 | (-0.11, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2515 |
| No | 411 | 200 | 48.7 | 410 | 193 | 47.1 | 0.6487 | 0.97 | ( 0.84, 1.12) | 0.94 | ( 0.71, 1.23) | -0.02 | (-0.08, 0.05) | |
| Yes | 1590 | 673 | 42.3 | 1642 | 610 | 37.1 | 0.0026 | 0.88 | ( 0.81, 0.96) | 0.81 | ( 0.70, 0.93) | -0.05 | (-0.09,-0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6352 |
| No | 282 | 125 | 44.3 | 277 | 115 | 41.5 | 0.5022 | 0.94 | ( 0.77, 1.13) | 0.89 | ( 0.64, 1.25) | -0.03 | (-0.11, 0.05) | |
| Yes | 1719 | 748 | 43.5 | 1775 | 688 | 38.8 | 0.0043 | 0.89 | ( 0.82, 0.96) | 0.82 | ( 0.72, 0.94) | -0.05 | (-0.08,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2788 |
| No | 229 | 84 | 36.7 | 250 | 93 | 37.2 | 0.9065 | 1.01 | ( 0.80, 1.28) | 1.02 | ( 0.71, 1.48) | 0.01 | (-0.08, 0.09) | |
| Yes | 1772 | 789 | 44.5 | 1802 | 710 | 39.4 | 0.0019 | 0.88 | ( 0.82, 0.96) | 0.81 | ( 0.71, 0.93) | -0.05 | (-0.08,-0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 727 | 36.3 | 2052 | 678 | 33.0 | 0.0277 | 0.91 | ( 0.84, | 0.99) | 0.86 | ( 0.76, | 0.98) | -0.03 | (-0.06, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.0779 |
| Male | 1065 | 386 | 36.2 | 1093 | 386 | 35.3 | 0.6528 | 0.97 | ( 0.87, | 1.09) | 0.96 | ( 0.81, | 1.15) | -0.01 | (-0.05, 0.03) | |
| Female | 936 | 341 | 36.4 | 959 | 292 | 30.4 | 0.0058 | 0.84 | ( 0.74, | 0.95) | 0.76 | ( 0.63, | 0.93) | -0.06 | (-0.10,-0.02) | |
| Age [years] | | | | | | | | | | | | | | | | 0.1400 |
| <65 | 331 | 145 | 43.8 | 313 | 141 | 45.0 | 0.7513 | 1.03 | ( 0.87, | 1.22) | 1.05 | ( 0.77, | 1.44) | 0.01 | (-0.06, 0.09) | |
| >=65 | 1670 | 582 | 34.9 | 1739 | 537 | 30.9 | 0.0136 | 0.89 | ( 0.80, | 0.98) | 0.84 | ( 0.72, | 0.96) | -0.04 | (-0.07,-0.01) | |
| Region | | | | | | | | | | | | | | | | 0.5455 |
| North America | 273 | 108 | 39.6 | 273 | 109 | 39.9 | 0.9303 | 1.01 | ( 0.82, | 1.24) | 1.02 | ( 0.72, | 1.43) | 0.00 | (-0.08, 0.09) | |
| Latin America | 511 | 207 | 40.5 | 504 | 184 | 36.5 | 0.1903 | 0.90 | ( 0.77, | 1.05) | 0.84 | ( 0.66, | 1.09) | -0.04 | (-0.10, 0.02) | |
| Europe | 865 | 272 | 31.4 | 894 | 235 | 26.3 | 0.0169 | 0.84 | ( 0.72, | 0.97) | 0.78 | ( 0.63, | 0.96) | -0.05 | (-0.09,-0.01) | |
| Asia | 231 | 85 | 36.8 | 248 | 91 | 36.7 | 0.9814 | 1.00 | ( 0.79, | 1.26) | 1.00 | ( 0.69, | 1.44) | 0.00 | (-0.09, 0.09) | |
| Other | 121 | 55 | 45.5 | 133 | 59 | 44.4 | 0.8611 | 0.98 | ( 0.74, | 1.28) | 0.96 | ( 0.58, | 1.57) | -0.01 | (-0.13, 0.11) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | | 0.5230 |
| Diabetic | 1045 | 460 | 44.0 | 1081 | 441 | 40.8 | 0.1327 | 0.93 | ( 0.84, | 1.02) | 0.88 | ( 0.74, | 1.04) | -0.03 | (-0.07, 0.01) | |
| Non-Diabetic | 956 | 267 | 27.9 | 971 | 237 | 24.4 | 0.0787 | 0.87 | ( 0.75, | 1.02) | 0.83 | ( 0.68, | 1.02) | -0.04 | (-0.07, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.9416 |
| <30 | 1086 | 392 | 36.1 | 1094 | 358 | 32.7 | 0.0975 | 0.91 | ( 0.81, | 1.02) | 0.86 | ( 0.72, | 1.03) | -0.03 | (-0.07, 0.01) | |
| >=30 | 915 | 335 | 36.6 | 958 | 320 | 33.4 | 0.1454 | 0.91 | ( 0.81, | 1.03) | 0.87 | ( 0.72, | 1.05) | -0.03 | (-0.08, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.7426 |
| <130 | 827 | 310 | 37.5 | 853 | 286 | 33.5 | 0.0902 | 0.89 | ( 0.79, | 1.02) | 0.84 | ( 0.69, | 1.03) | -0.04 | (-0.09, 0.01) | |
| >=130 | 1174 | 417 | 35.5 | 1199 | 392 | 32.7 | 0.1465 | 0.92 | ( 0.82, | 1.03) | 0.88 | ( 0.74, | 1.05) | -0.03 | (-0.07, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.7479 |
| <75 | 935 | 365 | 39.0 | 934 | 338 | 36.2 | 0.2036 | 0.93 | ( 0.82, | 1.04) | 0.89 | ( 0.73, | 1.07) | -0.03 | (-0.07, 0.02) | |
| 75 to <85 | 657 | 223 | 33.9 | 703 | 207 | 29.4 | 0.0747 | 0.87 | ( 0.74, | 1.01) | 0.81 | ( 0.65, | 1.02) | -0.04 | (-0.09, 0.00) | |
| >=85 | 409 | 139 | 34.0 | 415 | 133 | 32.0 | 0.5544 | 0.94 | ( 0.78, | 1.15) | 0.92 | ( 0.69, | 1.22) | -0.02 | (-0.08, 0.04) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2362 |
| <30 | 161 | 75 | 46.6 | 148 | 76 | 51.4 | 0.4023 | 1.10 | ( 0.88, 1.38) | 1.21 | ( 0.77, 1.89) | 0.05 | (-0.06, 0.16) | |
| 30 to <45 | 550 | 226 | 41.1 | 564 | 205 | 36.3 | 0.1041 | 0.88 | ( 0.76, 1.03) | 0.82 | ( 0.64, 1.04) | -0.05 | (-0.10, 0.01) | |
| >=45 | 1289 | 426 | 33.0 | 1340 | 397 | 29.6 | 0.0586 | 0.90 | ( 0.80, >1.00) | 0.85 | ( 0.72, 1.01) | -0.03 | (-0.07, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4266 |
| Normal (<30) | 764 | 252 | 33.0 | 787 | 223 | 28.3 | 0.0471 | 0.86 | ( 0.74, <1.00) | 0.80 | ( 0.65, 1.00) | -0.05 | (-0.09, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 329 | 35.7 | 938 | 307 | 32.7 | 0.1739 | 0.92 | ( 0.81, 1.04) | 0.88 | ( 0.72, 1.06) | -0.03 | (-0.07, 0.01) | |
| Macroalbuminuria (>300) | 311 | 144 | 46.3 | 318 | 147 | 46.2 | 0.9848 | 1.00 | ( 0.84, 1.18) | 1.00 | ( 0.73, 1.36) | 0.00 | (-0.08, 0.08) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0483 |
| Low, moderate or high | 1477 | 493 | 33.4 | 1548 | 448 | 28.9 | 0.0084 | 0.87 | ( 0.78, 0.96) | 0.81 | ( 0.70, 0.95) | -0.04 | (-0.08,-0.01) | |
| Very high | 519 | 233 | 44.9 | 495 | 229 | 46.3 | 0.6618 | 1.03 | ( 0.90, 1.18) | 1.06 | ( 0.83, 1.35) | 0.01 | (-0.05, 0.08) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3092 |
| No | 411 | 153 | 37.2 | 410 | 127 | 31.0 | 0.0589 | 0.83 | ( 0.69, 1.01) | 0.76 | ( 0.57, 1.01) | -0.06 | (-0.13, 0.00) | |
| Yes | 1590 | 574 | 36.1 | 1642 | 551 | 33.6 | 0.1291 | 0.93 | ( 0.85, 1.02) | 0.89 | ( 0.77, 1.03) | -0.03 | (-0.06, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4996 |
| No | 282 | 89 | 31.6 | 277 | 73 | 26.4 | 0.1749 | 0.84 | ( 0.64, 1.08) | 0.78 | ( 0.54, 1.12) | -0.05 | (-0.13, 0.02) | |
| Yes | 1719 | 638 | 37.1 | 1775 | 605 | 34.1 | 0.0614 | 0.92 | ( 0.84, >1.00) | 0.88 | ( 0.76, 1.01) | -0.03 | (-0.06, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4226 |
| No | 229 | 75 | 32.8 | 250 | 67 | 26.8 | 0.1543 | 0.82 | ( 0.62, 1.08) | 0.75 | ( 0.51, 1.11) | -0.06 | (-0.14, 0.02) | |
| Yes | 1772 | 652 | 36.8 | 1802 | 611 | 33.9 | 0.0710 | 0.92 | ( 0.84, 1.01) | 0.88 | ( 0.77, 1.01) | -0.03 | (-0.06, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 558 | 27.9 | 2052 | 548 | 26.7 | 0.3990 | 0.96 | ( 0.87, 1.06) | 0.94 | ( 0.82, 1.08) | -0.01 | (-0.04, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 486 | 24.3 | 2052 | 488 | 23.8 | 0.7061 | 0.98 ( 0.88, 1.09) | 0.97 ( 0.84, 1.12) | -0.01 (-0.03, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 459 | 22.9 | 2052 | 487 | 23.7 | 0.5500 | 1.03 | ( 0.93, 1.16) | 1.05 | ( 0.90, 1.21) | 0.01 (-0.02, 0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 452 | 22.6 | 2052 | 410 | 20.0 | 0.0425 | 0.88 | ( 0.79, <1.00) | 0.86 | ( 0.74, 0.99) | -0.03 | (-0.05, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.2016 |
| Male | 1065 | 219 | 20.6 | 1093 | 183 | 16.7 | 0.0227 | 0.81 | ( 0.68, 0.97) | 0.78 | ( 0.63, 0.97) | -0.04 | (-0.07,-0.01) | |
| Female | 936 | 233 | 24.9 | 959 | 227 | 23.7 | 0.5348 | 0.95 | ( 0.81, 1.11) | 0.94 | ( 0.76, 1.15) | -0.01 | (-0.05, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.5043 |
| <65 | 331 | 69 | 20.8 | 313 | 52 | 16.6 | 0.1693 | 0.80 | ( 0.58, 1.10) | 0.76 | ( 0.51, 1.13) | -0.04 | (-0.10, 0.02) | |
| >=65 | 1670 | 383 | 22.9 | 1739 | 358 | 20.6 | 0.0967 | 0.90 | ( 0.79, 1.02) | 0.87 | ( 0.74, 1.03) | -0.02 | (-0.05, 0.00) | |
| Region | | | | | | | | | | | | | | 0.4988 |
| North America | 273 | 104 | 38.1 | 273 | 84 | 30.8 | 0.0716 | 0.81 | ( 0.64, 1.02) | 0.72 | ( 0.51, 1.03) | -0.07 | (-0.15, 0.01) | |
| Latin America | 511 | 86 | 16.8 | 504 | 85 | 16.9 | 0.9880 | 1.00 | ( 0.76, 1.32) | 1.00 | ( 0.72, 1.39) | 0.00 | (-0.05, 0.05) | |
| Europe | 865 | 152 | 17.6 | 894 | 149 | 16.7 | 0.6141 | 0.95 | ( 0.77, 1.17) | 0.94 | ( 0.73, 1.20) | -0.01 | (-0.04, 0.03) | |
| Asia | 231 | 87 | 37.7 | 248 | 70 | 28.2 | 0.0279 | 0.75 | ( 0.58, 0.97) | 0.65 | ( 0.44, 0.96) | -0.09 | (-0.18,-0.01) | |
| Other | 121 | 23 | 19.0 | 133 | 22 | 16.5 | 0.6070 | 0.87 | ( 0.51, 1.48) | 0.84 | ( 0.44, 1.61) | -0.02 | (-0.12, 0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2644 |
| Diabetic | 1045 | 223 | 21.3 | 1081 | 218 | 20.2 | 0.5048 | 0.95 | ( 0.80, 1.12) | 0.93 | ( 0.75, 1.15) | -0.01 | (-0.05, 0.02) | |
| Non-Diabetic | 956 | 229 | 24.0 | 971 | 192 | 19.8 | 0.0264 | 0.83 | ( 0.70, 0.98) | 0.78 | ( 0.63, 0.97) | -0.04 | (-0.08, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9376 |
| <30 | 1086 | 237 | 21.8 | 1094 | 212 | 19.4 | 0.1582 | 0.89 | ( 0.75, 1.05) | 0.86 | ( 0.70, 1.06) | -0.02 | (-0.06, 0.01) | |
| >=30 | 915 | 215 | 23.5 | 958 | 198 | 20.7 | 0.1399 | 0.88 | ( 0.74, 1.04) | 0.85 | ( 0.68, 1.06) | -0.03 | (-0.07, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7539 |
| <130 | 827 | 192 | 23.2 | 853 | 179 | 21.0 | 0.2703 | 0.90 | ( 0.76, 1.08) | 0.88 | ( 0.70, 1.11) | -0.02 | (-0.06, 0.02) | |
| >=130 | 1174 | 260 | 22.1 | 1199 | 231 | 19.3 | 0.0833 | 0.87 | ( 0.74, 1.02) | 0.84 | ( 0.69, 1.02) | -0.03 | (-0.06, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3583 |
| <75 | 935 | 225 | 24.1 | 934 | 215 | 23.0 | 0.5945 | 0.96 | ( 0.81, 1.13) | 0.94 | ( 0.76, 1.17) | -0.01 | (-0.05, 0.03) | |
| 75 to <85 | 657 | 134 | 20.4 | 703 | 123 | 17.5 | 0.1723 | 0.86 | ( 0.69, 1.07) | 0.83 | ( 0.63, 1.09) | -0.03 | (-0.07, 0.01) | |
| >=85 | 409 | 93 | 22.7 | 415 | 72 | 17.3 | 0.0533 | 0.76 | ( 0.58, 1.01) | 0.71 | ( 0.51, 1.01) | -0.05 | (-0.11, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5946 |
| <30 | 161 | 40 | 24.8 | 148 | 39 | 26.4 | 0.7617 | 1.06 | ( 0.73, 1.55) | 1.08 | ( 0.65, 1.80) | 0.02 | (-0.08, 0.11) | |
| 30 to <45 | 550 | 135 | 24.5 | 564 | 124 | 22.0 | 0.3120 | 0.90 | ( 0.72, 1.11) | 0.87 | ( 0.66, 1.14) | -0.03 | (-0.08, 0.02) | |
| >=45 | 1289 | 277 | 21.5 | 1340 | 247 | 18.4 | 0.0498 | 0.86 | ( 0.74, >1.00) | 0.83 | ( 0.68, 1.00) | -0.03 | (-0.06, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7047 |
| Normal (<30) | 764 | 188 | 24.6 | 787 | 161 | 20.5 | 0.0504 | 0.83 | ( 0.69, >1.00) | 0.79 | ( 0.62, 1.00) | -0.04 | (-0.08, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 195 | 21.2 | 938 | 182 | 19.4 | 0.3427 | 0.92 | ( 0.77, 1.10) | 0.90 | ( 0.71, 1.12) | -0.02 | (-0.05, 0.02) | |
| Macroalbuminuria (>300) | 311 | 67 | 21.5 | 318 | 64 | 20.1 | 0.6616 | 0.93 | ( 0.69, 1.27) | 0.92 | ( 0.62, 1.35) | -0.01 | (-0.08, 0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1572 |
| Low, moderate or high | 1477 | 330 | 22.3 | 1548 | 290 | 18.7 | 0.0140 | 0.84 | ( 0.73, 0.97) | 0.80 | ( 0.67, 0.96) | -0.04 | (-0.06,-0.01) | |
| Very high | 519 | 121 | 23.3 | 495 | 117 | 23.6 | 0.9037 | 1.01 | ( 0.81, 1.27) | 1.02 | ( 0.76, 1.36) | 0.00 | (-0.05, 0.06) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4605 |
| No | 411 | 115 | 28.0 | 410 | 94 | 22.9 | 0.0965 | 0.82 | ( 0.65, 1.04) | 0.77 | ( 0.56, 1.05) | -0.05 | (-0.11, 0.01) | |
| Yes | 1590 | 337 | 21.2 | 1642 | 316 | 19.2 | 0.1675 | 0.91 | ( 0.79, 1.04) | 0.89 | ( 0.75, 1.05) | -0.02 | (-0.05, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5832 |
| No | 282 | 57 | 20.2 | 277 | 54 | 19.5 | 0.8315 | 0.96 | ( 0.69, 1.35) | 0.96 | ( 0.63, 1.45) | -0.01 | (-0.07, 0.06) | |
| Yes | 1719 | 395 | 23.0 | 1775 | 356 | 20.1 | 0.0355 | 0.87 | ( 0.77, 0.99) | 0.84 | ( 0.72, 0.99) | -0.03 | (-0.06, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1603 |
| No | 229 | 44 | 19.2 | 250 | 54 | 21.6 | 0.5179 | 1.12 | ( 0.79, 1.60) | 1.16 | ( 0.74, 1.81) | 0.02 | (-0.05, 0.10) | |
| Yes | 1772 | 408 | 23.0 | 1802 | 356 | 19.8 | 0.0172 | 0.86 | ( 0.76, 0.97) | 0.82 | ( 0.70, 0.97) | -0.03 | (-0.06,-0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 402 | 20.1 | 2052 | 450 | 21.9 | 0.1507 | 1.09 ( 0.97, 1.23) | 1.12 ( 0.96, 1.30) | 0.02 (-0.01, 0.04) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 394 | 19.7 | 2052 | 365 | 17.8 | 0.1206 | 0.90 | ( 0.79, 1.03) | 0.88 | ( 0.75, 1.03) | -0.02 | (-0.04, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 350 | 17.5 | 2052 | 381 | 18.6 | 0.3731 | 1.06 | ( 0.93, 1.21) | 1.08 | ( 0.92, 1.26) | 0.01 | (-0.01, 0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 351 | 17.5 | 2052 | 371 | 18.1 | 0.6541 | 1.03 | ( 0.90, 1.18) | 1.04 | ( 0.88, 1.22) | 0.01 | (-0.02, 0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 283 | 14.1 | 2052 | 225 | 11.0 | 0.0023 | 0.78 | ( 0.66, 0.91) | 0.75 | ( 0.62, 0.90) | -0.03 | (-0.05,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.5712 |
| Male | 1065 | 165 | 15.5 | 1093 | 126 | 11.5 | 0.0070 | 0.74 | ( 0.60, 0.92) | 0.71 | ( 0.55, 0.91) | -0.04 | (-0.07,-0.01) | |
| Female | 936 | 118 | 12.6 | 959 | 99 | 10.3 | 0.1186 | 0.82 | ( 0.64, 1.05) | 0.80 | ( 0.60, 1.06) | -0.02 | (-0.05, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.8453 |
| <65 | 331 | 42 | 12.7 | 313 | 32 | 10.2 | 0.3269 | 0.81 | ( 0.52, 1.24) | 0.78 | ( 0.48, 1.28) | -0.02 | (-0.07, 0.02) | |
| >=65 | 1670 | 241 | 14.4 | 1739 | 193 | 11.1 | 0.0035 | 0.77 | ( 0.64, 0.92) | 0.74 | ( 0.60, 0.91) | -0.03 | (-0.06,-0.01) | |
| Region | | | | | | | | | | | | | | 0.0114 |
| North America | 273 | 52 | 19.0 | 273 | 25 | 9.2 | 0.0009 | 0.48 | ( 0.31, 0.75) | 0.43 | ( 0.26, 0.71) | -0.10 | (-0.16,-0.04) | |
| Latin America | 511 | 66 | 12.9 | 504 | 67 | 13.3 | 0.8585 | 1.03 | ( 0.75, 1.41) | 1.03 | ( 0.72, 1.49) | 0.00 | (-0.04, 0.05) | |
| Europe | 865 | 114 | 13.2 | 894 | 75 | 8.4 | 0.0012 | 0.64 | ( 0.48, 0.84) | 0.60 | ( 0.44, 0.82) | -0.05 | (-0.08,-0.02) | |
| Asia | 231 | 35 | 15.2 | 248 | 43 | 17.3 | 0.5171 | 1.14 | ( 0.76, 1.72) | 1.17 | ( 0.72, 1.91) | 0.02 | (-0.04, 0.09) | |
| Other | 121 | 16 | 13.2 | 133 | 15 | 11.3 | 0.6363 | 0.85 | ( 0.44, 1.65) | 0.83 | ( 0.39, 1.77) | -0.02 | (-0.10, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0265 |
| Diabetic | 1045 | 150 | 14.4 | 1081 | 141 | 13.0 | 0.3794 | 0.91 | ( 0.73, 1.13) | 0.90 | ( 0.70, 1.15) | -0.01 | (-0.04, 0.02) | |
| Non-Diabetic | 956 | 133 | 13.9 | 971 | 84 | 8.7 | 0.0003 | 0.62 | ( 0.48, 0.80) | 0.59 | ( 0.44, 0.78) | -0.05 | (-0.08,-0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1652 |
| <30 | 1086 | 160 | 14.7 | 1094 | 138 | 12.6 | 0.1499 | 0.86 | ( 0.69, 1.06) | 0.84 | ( 0.65, 1.07) | -0.02 | (-0.05, 0.01) | |
| >=30 | 915 | 123 | 13.4 | 958 | 87 | 9.1 | 0.0028 | 0.68 | ( 0.52, 0.88) | 0.64 | ( 0.48, 0.86) | -0.04 | (-0.07,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5581 |
| <130 | 827 | 112 | 13.5 | 853 | 95 | 11.1 | 0.1337 | 0.82 | ( 0.64, 1.06) | 0.80 | ( 0.60, 1.07) | -0.02 | (-0.06, 0.01) | |
| >=130 | 1174 | 171 | 14.6 | 1199 | 130 | 10.8 | 0.0064 | 0.74 | ( 0.60, 0.92) | 0.71 | ( 0.56, 0.91) | -0.04 | (-0.06,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7859 |
| <75 | 935 | 152 | 16.3 | 934 | 113 | 12.1 | 0.0100 | 0.74 | ( 0.59, 0.93) | 0.71 | ( 0.55, 0.92) | -0.04 | (-0.07,-0.01) | |
| 75 to <85 | 657 | 84 | 12.8 | 703 | 76 | 10.8 | 0.2587 | 0.85 | ( 0.63, 1.13) | 0.83 | ( 0.59, 1.15) | -0.02 | (-0.05, 0.01) | |
| >=85 | 409 | 47 | 11.5 | 415 | 36 | 8.7 | 0.1792 | 0.75 | ( 0.50, 1.14) | 0.73 | ( 0.46, 1.16) | -0.03 | (-0.07, 0.01) | |

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Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.5599 |
| <30 | 161 | 38 | 23.6 | 148 | 33 | 22.3 | 0.7853 | 0.94 | ( 0.63, | 1.42) | 0.93 | ( 0.55, | 1.58) | -0.01 | (-0.11, 0.08) | |
| 30 to <45 | 550 | 86 | 15.6 | 564 | 63 | 11.2 | 0.0286 | 0.71 | ( 0.53, | 0.97) | 0.68 | ( 0.48, | 0.96) | -0.04 | (-0.08, 0.00) | |
| >=45 | 1289 | 159 | 12.3 | 1340 | 129 | 9.6 | 0.0262 | 0.78 | ( 0.63, | 0.97) | 0.76 | ( 0.59, | 0.97) | -0.03 | (-0.05, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.5249 |
| Normal (<30) | 764 | 99 | 13.0 | 787 | 78 | 9.9 | 0.0592 | 0.76 | ( 0.58, | 1.01) | 0.74 | ( 0.54, | 1.01) | -0.03 | (-0.06, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 133 | 14.4 | 938 | 99 | 10.6 | 0.0112 | 0.73 | ( 0.57, | 0.93) | 0.70 | ( 0.53, | 0.92) | -0.04 | (-0.07,-0.01) | |
| Macroalbuminuria (>300) | 311 | 50 | 16.1 | 318 | 48 | 15.1 | 0.7340 | 0.94 | ( 0.65, | 1.35) | 0.93 | ( 0.60, | 1.43) | -0.01 | (-0.07, 0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.3482 |
| Low, moderate or high | 1477 | 188 | 12.7 | 1548 | 146 | 9.4 | 0.0038 | 0.74 | ( 0.60, | 0.91) | 0.71 | ( 0.57, | 0.90) | -0.03 | (-0.06,-0.01) | |
| Very high | 519 | 95 | 18.3 | 495 | 79 | 16.0 | 0.3222 | 0.87 | ( 0.66, | 1.14) | 0.85 | ( 0.61, | 1.18) | -0.02 | (-0.07, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | | | 0.2585 |
| No | 411 | 61 | 14.8 | 410 | 56 | 13.7 | 0.6277 | 0.92 | ( 0.66, | 1.29) | 0.91 | ( 0.61, | 1.34) | -0.01 | (-0.06, 0.04) | |
| Yes | 1590 | 222 | 14.0 | 1642 | 169 | 10.3 | 0.0014 | 0.74 | ( 0.61, | 0.89) | 0.71 | ( 0.57, | 0.87) | -0.04 | (-0.06,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.1060 |
| No | 282 | 48 | 17.0 | 277 | 26 | 9.4 | 0.0077 | 0.55 | ( 0.35, | 0.86) | 0.50 | ( 0.30, | 0.84) | -0.08 | (-0.13,-0.02) | |
| Yes | 1719 | 235 | 13.7 | 1775 | 199 | 11.2 | 0.0276 | 0.82 | ( 0.69, | 0.98) | 0.80 | ( 0.65, | 0.98) | -0.02 | (-0.05, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.6422 |
| No | 229 | 24 | 10.5 | 250 | 23 | 9.2 | 0.6380 | 0.88 | ( 0.51, | 1.51) | 0.87 | ( 0.47, | 1.58) | -0.01 | (-0.07, 0.04) | |
| Yes | 1772 | 259 | 14.6 | 1802 | 202 | 11.2 | 0.0024 | 0.77 | ( 0.65, | 0.91) | 0.74 | ( 0.61, | 0.90) | -0.03 | (-0.06,-0.01) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 277 | 13.8 | 2052 | 244 | 11.9 | 0.0634 | 0.86 ( 0.73, 1.01) | 0.84 ( 0.70, 1.01) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 207 | 10.3 | 2052 | 255 | 12.4 | 0.0370 | 1.20 | ( 1.01, 1.43) | 1.23 | ( 1.01, 1.49) | 0.02 | ( 0.00, 0.04) | |
| Sex | | | | | | | | | | | | | | 0.1866 |
| Male | 1065 | 111 | 10.4 | 1093 | 122 | 11.2 | 0.5800 | 1.07 | ( 0.84, 1.37) | 1.08 | ( 0.82, 1.42) | 0.01 | (-0.02, 0.03) | |
| Female | 936 | 96 | 10.3 | 959 | 133 | 13.9 | 0.0159 | 1.35 | ( 1.06, 1.73) | 1.41 | ( 1.07, 1.86) | 0.04 | ( 0.01, 0.07) | |
| Age [years] | | | | | | | | | | | | | | 0.5344 |
| <65 | 331 | 26 | 7.9 | 313 | 34 | 10.9 | 0.1894 | 1.38 | ( 0.85, 2.25) | 1.43 | ( 0.84, 2.44) | 0.03 | (-0.01, 0.08) | |
| >=65 | 1670 | 181 | 10.8 | 1739 | 221 | 12.7 | 0.0906 | 1.17 | ( 0.97, 1.41) | 1.20 | ( 0.97, 1.48) | 0.02 | ( 0.00, 0.04) | |
| Region | | | | | | | | | | | | | | 0.6747 |
| North America | 273 | 39 | 14.3 | 273 | 51 | 18.7 | 0.1663 | 1.31 | ( 0.89, 1.92) | 1.38 | ( 0.87, 2.17) | 0.04 | (-0.02, 0.11) | |
| Latin America | 511 | 31 | 6.1 | 504 | 42 | 8.3 | 0.1622 | 1.37 | ( 0.88, 2.15) | 1.41 | ( 0.87, 2.28) | 0.02 | (-0.01, 0.05) | |
| Europe | 865 | 79 | 9.1 | 894 | 88 | 9.8 | 0.6113 | 1.08 | ( 0.81, 1.44) | 1.09 | ( 0.79, 1.49) | 0.01 | (-0.02, 0.03) | |
| Asia | 231 | 42 | 18.2 | 248 | 59 | 23.8 | 0.1327 | 1.31 | ( 0.92, 1.86) | 1.40 | ( 0.90, 2.19) | 0.06 | (-0.02, 0.13) | |
| Other | 121 | 16 | 13.2 | 133 | 15 | 11.3 | 0.6363 | 0.85 | ( 0.44, 1.65) | 0.83 | ( 0.39, 1.77) | -0.02 | (-0.10, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.1043 |
| Diabetic | 1045 | 125 | 12.0 | 1081 | 137 | 12.7 | 0.6177 | 1.06 | ( 0.84, 1.33) | 1.07 | ( 0.82, 1.38) | 0.01 | (-0.02, 0.04) | |
| Non-Diabetic | 956 | 82 | 8.6 | 971 | 118 | 12.2 | 0.0101 | 1.42 | ( 1.08, 1.85) | 1.47 | ( 1.10, 1.98) | 0.04 | ( 0.01, 0.06) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8256 |
| <30 | 1086 | 116 | 10.7 | 1094 | 138 | 12.6 | 0.1596 | 1.18 | ( 0.94, 1.49) | 1.21 | ( 0.93, 1.57) | 0.02 | (-0.01, 0.05) | |
| >=30 | 915 | 91 | 9.9 | 958 | 117 | 12.2 | 0.1185 | 1.23 | ( 0.95, 1.59) | 1.26 | ( 0.94, 1.68) | 0.02 | (-0.01, 0.05) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3919 |
| <130 | 827 | 90 | 10.9 | 853 | 102 | 12.0 | 0.4887 | 1.10 | ( 0.84, 1.43) | 1.11 | ( 0.82, 1.50) | 0.01 | (-0.02, 0.04) | |
| >=130 | 1174 | 117 | 10.0 | 1199 | 153 | 12.8 | 0.0321 | 1.28 | ( 1.02, 1.61) | 1.32 | ( 1.02, 1.71) | 0.03 | ( 0.00, 0.05) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8818 |
| <75 | 935 | 101 | 10.8 | 934 | 126 | 13.5 | 0.0753 | 1.25 | ( 0.98, 1.60) | 1.29 | ( 0.97, 1.70) | 0.03 | ( 0.00, 0.06) | |
| 75 to <85 | 657 | 66 | 10.0 | 703 | 84 | 11.9 | 0.2629 | 1.19 | ( 0.88, 1.61) | 1.22 | ( 0.86, 1.71) | 0.02 | (-0.01, 0.05) | |
| >=85 | 409 | 40 | 9.8 | 415 | 45 | 10.8 | 0.6158 | 1.11 | ( 0.74, 1.66) | 1.12 | ( 0.72, 1.76) | 0.01 | (-0.03, 0.05) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.1179 |
| <30 | 161 | 24 | 14.9 | 148 | 25 | 16.9 | 0.6332 | 1.13 | ( 0.68, | 1.89) | 1.16 | ( 0.63, | 2.14) | 0.02 | (-0.06, 0.10) | |
| 30 to <45 | 550 | 67 | 12.2 | 564 | 63 | 11.2 | 0.5990 | 0.92 | ( 0.66, | 1.27) | 0.91 | ( 0.63, | 1.31) | -0.01 | (-0.05, 0.03) | |
| >=45 | 1289 | 116 | 9.0 | 1340 | 167 | 12.5 | 0.0042 | 1.38 | ( 1.11, | 1.73) | 1.44 | ( 1.12, | 1.85) | 0.03 | ( 0.01, 0.06) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.1078 |
| Normal (<30) | 764 | 85 | 11.1 | 787 | 84 | 10.7 | 0.7751 | 0.96 | ( 0.72, | 1.28) | 0.95 | ( 0.69, | 1.31) | 0.00 | (-0.04, 0.03) | |
| Microalbuminuria (30 to <=300) | 921 | 86 | 9.3 | 938 | 127 | 13.5 | 0.0045 | 1.45 | ( 1.12, | 1.88) | 1.52 | ( 1.14, | 2.03) | 0.04 | ( 0.01, 0.07) | |
| Macroalbuminuria (>300) | 311 | 36 | 11.6 | 318 | 43 | 13.5 | 0.4614 | 1.17 | ( 0.77, | 1.77) | 1.19 | ( 0.74, | 1.92) | 0.02 | (-0.03, 0.07) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.4097 |
| Low, moderate or high | 1477 | 139 | 9.4 | 1548 | 184 | 11.9 | 0.0276 | 1.26 | ( 1.03, | 1.56) | 1.30 | ( 1.03, | 1.64) | 0.02 | ( 0.00, 0.05) | |
| Very high | 519 | 68 | 13.1 | 495 | 70 | 14.1 | 0.6295 | 1.08 | ( 0.79, | 1.47) | 1.09 | ( 0.76, | 1.56) | 0.01 | (-0.03, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | | | 0.0822 |
| No | 411 | 43 | 10.5 | 410 | 68 | 16.6 | 0.0103 | 1.59 | ( 1.11, | 2.26) | 1.70 | ( 1.13, | 2.56) | 0.06 | ( 0.01, 0.11) | |
| Yes | 1590 | 164 | 10.3 | 1642 | 187 | 11.4 | 0.3265 | 1.10 | ( 0.91, | 1.35) | 1.12 | ( 0.90, | 1.40) | 0.01 | (-0.01, 0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.6235 |
| No | 282 | 32 | 11.3 | 277 | 34 | 12.3 | 0.7342 | 1.08 | ( 0.69, | 1.70) | 1.09 | ( 0.65, | 1.83) | 0.01 | (-0.04, 0.06) | |
| Yes | 1719 | 175 | 10.2 | 1775 | 221 | 12.5 | 0.0343 | 1.22 | ( 1.01, | 1.47) | 1.25 | ( 1.02, | 1.55) | 0.02 | ( 0.00, 0.04) | |
| Baseline use of diuretics | | | | | | | | | | | | | | | | 0.2138 |
| No | 229 | 23 | 10.0 | 250 | 40 | 16.0 | 0.0540 | 1.59 | ( 0.99, | 2.58) | 1.71 | ( 0.99, | 2.95) | 0.06 | ( 0.00, 0.12) | |
| Yes | 1772 | 184 | 10.4 | 1802 | 215 | 11.9 | 0.1419 | 1.15 | ( 0.95, | 1.38) | 1.17 | ( 0.95, | 1.44) | 0.02 | (-0.01, 0.04) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 166 | 8.3 | 2052 | 166 | 8.1 | 0.8109 | 0.98 ( 0.79, 1.20) | 0.97 ( 0.78, 1.22) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 151 | 7.5 | 2052 | 166 | 8.1 | 0.5194 | 1.07 | ( 0.87, 1.32) | 1.08 | ( 0.86, 1.36) | 0.01 | (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 110 | 5.5 | 2052 | 138 | 6.7 | 0.1030 | 1.22 ( 0.96, 1.56) | 1.24 ( 0.96, 1.61) | 0.01 ( 0.00, 0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 119 | 5.9 | 2052 | 101 | 4.9 | 0.1499 | 0.83 | ( 0.64, 1.07) | 0.82 | ( 0.62, 1.08) | -0.01 | (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Reproductive system and breast disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 85 | 4.2 | 2052 | 90 | 4.4 | 0.8288 | 1.03 ( 0.77, 1.38) | 1.03 ( 0.76, 1.40) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Ear and labyrinth disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 2001 | 63 | 3.1 | 2052 | 78 | 3.8 | 0.2569 | 1.21 | ( 0.87, 1.67) | 1.22 | ( 0.87, 1.70) | 0.01 | ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Endocrine disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 62 | 3.1 | 2052 | 58 | 2.8 | 0.6096 | 0.91 ( 0.64, 1.30) | 0.91 ( 0.63, 1.31) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Immune system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 22 | 1.1 | 2052 | 11 | 0.5 | 0.0460 | 0.49 ( 0.24, >1.00) | 0.48 ( 0.23, 1.00) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 749 | 37.4 | 2052 | 655 | 31.9 | 0.0002 | 0.85 | ( 0.78, 0.93) | 0.78 | ( 0.69, 0.89) | -0.06 | (-0.08,-0.03) | |
| Sex | | | | | | | | | | | | | | 0.2239 |
| Male | 1065 | 423 | 39.7 | 1093 | 353 | 32.3 | 0.0003 | 0.81 | ( 0.73, 0.91) | 0.72 | ( 0.61, 0.86) | -0.07 | (-0.11,-0.03) | |
| Female | 936 | 326 | 34.8 | 959 | 302 | 31.5 | 0.1227 | 0.90 | ( 0.80, 1.03) | 0.86 | ( 0.71, 1.04) | -0.03 | (-0.08, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.0215 |
| <65 | 331 | 100 | 30.2 | 313 | 103 | 32.9 | 0.4617 | 1.09 | ( 0.87, 1.37) | 1.13 | ( 0.81, 1.58) | 0.03 | (-0.04, 0.10) | |
| >=65 | 1670 | 649 | 38.9 | 1739 | 552 | 31.7 | <0.0001 | 0.82 | ( 0.75, 0.90) | 0.73 | ( 0.64, 0.84) | -0.07 | (-0.10,-0.04) | |
| Region | | | | | | | | | | | | | | 0.8506 |
| North America | 273 | 133 | 48.7 | 273 | 117 | 42.9 | 0.1693 | 0.88 | ( 0.73, 1.06) | 0.79 | ( 0.56, 1.11) | -0.06 | (-0.14, 0.02) | |
| Latin America | 511 | 184 | 36.0 | 504 | 156 | 31.0 | 0.0880 | 0.86 | ( 0.72, 1.02) | 0.80 | ( 0.61, 1.03) | -0.05 | (-0.11, 0.01) | |
| Europe | 865 | 301 | 34.8 | 894 | 263 | 29.4 | 0.0157 | 0.85 | ( 0.74, 0.97) | 0.78 | ( 0.64, 0.95) | -0.05 | (-0.10,-0.01) | |
| Asia | 231 | 85 | 36.8 | 248 | 83 | 33.5 | 0.4455 | 0.91 | ( 0.71, 1.16) | 0.86 | ( 0.59, 1.26) | -0.03 | (-0.12, 0.05) | |
| Other | 121 | 46 | 38.0 | 133 | 36 | 27.1 | 0.0623 | 0.71 | ( 0.50, 1.02) | 0.61 | ( 0.36, 1.03) | -0.11 | (-0.22, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0862 |
| Diabetic | 1045 | 428 | 41.0 | 1081 | 353 | 32.7 | <0.0001 | 0.80 | ( 0.71, 0.89) | 0.70 | ( 0.59, 0.83) | -0.08 | (-0.12,-0.04) | |
| Non-Diabetic | 956 | 321 | 33.6 | 971 | 302 | 31.1 | 0.2454 | 0.93 | ( 0.81, 1.05) | 0.89 | ( 0.74, 1.08) | -0.02 | (-0.07, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6441 |
| <30 | 1086 | 416 | 38.3 | 1094 | 351 | 32.1 | 0.0024 | 0.84 | ( 0.75, 0.94) | 0.76 | ( 0.64, 0.91) | -0.06 | (-0.10,-0.02) | |
| >=30 | 915 | 333 | 36.4 | 958 | 304 | 31.7 | 0.0333 | 0.87 | ( 0.77, 0.99) | 0.81 | ( 0.67, 0.98) | -0.05 | (-0.09, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4352 |
| <130 | 827 | 323 | 39.1 | 853 | 295 | 34.6 | 0.0573 | 0.89 | ( 0.78, >1.00) | 0.82 | ( 0.68, 1.01) | -0.04 | (-0.09, 0.00) | |
| >=130 | 1174 | 426 | 36.3 | 1199 | 360 | 30.0 | 0.0012 | 0.83 | ( 0.74, 0.93) | 0.75 | ( 0.63, 0.89) | -0.06 | (-0.10,-0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1719 |
| <75 | 935 | 358 | 38.3 | 934 | 331 | 35.4 | 0.2016 | 0.93 | ( 0.82, 1.04) | 0.88 | ( 0.73, 1.07) | -0.03 | (-0.07, 0.02) | |
| 75 to <85 | 657 | 247 | 37.6 | 703 | 205 | 29.2 | 0.0010 | 0.78 | ( 0.67, 0.90) | 0.68 | ( 0.54, 0.86) | -0.08 | (-0.13,-0.03) | |
| >=85 | 409 | 144 | 35.2 | 415 | 119 | 28.7 | 0.0443 | 0.81 | ( 0.67, <1.00) | 0.74 | ( 0.55, 0.99) | -0.07 | (-0.13, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.4162 |
| <30 | 161 | 76 | 47.2 | 148 | 69 | 46.6 | 0.9182 | 0.99 ( 0.78, 1.25) | 0.98 ( 0.62, 1.53) | -0.01 (-0.12, 0.11) | |
| 30 to <45 | 550 | 228 | 41.5 | 564 | 203 | 36.0 | 0.0613 | 0.87 ( 0.75, 1.01) | 0.79 ( 0.62, 1.01) | -0.05 (-0.11, 0.00) | |
| >=45 | 1289 | 445 | 34.5 | 1340 | 383 | 28.6 | 0.0010 | 0.83 ( 0.74, 0.93) | 0.76 ( 0.64, 0.90) | -0.06 (-0.09,-0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.9096 |
| Normal (<30) | 764 | 256 | 33.5 | 787 | 227 | 28.8 | 0.0474 | 0.86 ( 0.74, <1.00) | 0.80 ( 0.65, 1.00) | -0.05 (-0.09, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 354 | 38.4 | 938 | 311 | 33.2 | 0.0175 | 0.86 ( 0.76, 0.97) | 0.79 ( 0.66, 0.96) | -0.05 (-0.10,-0.01) | |
| Macroalbuminuria (>300) | 311 | 138 | 44.4 | 318 | 116 | 36.5 | 0.0436 | 0.82 ( 0.68, <1.00) | 0.72 ( 0.52, 0.99) | -0.08 (-0.16, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.4733 |
| Low, moderate or high | 1477 | 511 | 34.6 | 1548 | 451 | 29.1 | 0.0013 | 0.84 ( 0.76, 0.94) | 0.78 ( 0.67, 0.91) | -0.05 (-0.09,-0.02) | |
| Very high | 519 | 237 | 45.7 | 495 | 203 | 41.0 | 0.1349 | 0.90 ( 0.78, 1.03) | 0.83 ( 0.64, 1.06) | -0.05 (-0.11, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.2622 |
| No | 411 | 175 | 42.6 | 410 | 162 | 39.5 | 0.3718 | 0.93 ( 0.79, 1.09) | 0.88 ( 0.67, 1.16) | -0.03 (-0.10, 0.04) | |
| Yes | 1590 | 574 | 36.1 | 1642 | 493 | 30.0 | 0.0002 | 0.83 ( 0.75, 0.92) | 0.76 ( 0.66, 0.88) | -0.06 (-0.09,-0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6194 |
| No | 282 | 110 | 39.0 | 277 | 97 | 35.0 | 0.3288 | 0.90 ( 0.72, 1.12) | 0.84 ( 0.60, 1.19) | -0.04 (-0.12, 0.04) | |
| Yes | 1719 | 639 | 37.2 | 1775 | 558 | 31.4 | 0.0004 | 0.85 ( 0.77, 0.93) | 0.77 ( 0.67, 0.89) | -0.06 (-0.09,-0.03) | |
| Baseline use of diuretics | | | | | | | | | | | 0.8138 |
| No | 229 | 72 | 31.4 | 250 | 65 | 26.0 | 0.1881 | 0.83 ( 0.62, 1.10) | 0.77 ( 0.52, 1.14) | -0.05 (-0.14, 0.03) | |
| Yes | 1772 | 677 | 38.2 | 1802 | 590 | 32.7 | 0.0006 | 0.86 ( 0.78, 0.94) | 0.79 ( 0.69, 0.90) | -0.05 (-0.09,-0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 340 | 17.0 | 2052 | 332 | 16.2 | 0.4870 | 0.95 | ( 0.83, 1.09) | 0.94 | ( 0.80, 1.11) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 217 | 10.8 | 2052 | 178 | 8.7 | 0.0199 | 0.80 | ( 0.66, 0.97) | 0.78 | ( 0.63, 0.96) | -0.02 | (-0.04, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.9800 |
| Male | 1065 | 124 | 11.6 | 1093 | 102 | 9.3 | 0.0796 | 0.80 | ( 0.63, 1.03) | 0.78 | ( 0.59, 1.03) | -0.02 | (-0.05, 0.00) | |
| Female | 936 | 93 | 9.9 | 959 | 76 | 7.9 | 0.1246 | 0.80 | ( 0.60, 1.07) | 0.78 | ( 0.57, 1.07) | -0.02 | (-0.05, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3872 |
| <65 | 331 | 34 | 10.3 | 313 | 31 | 9.9 | 0.8769 | 0.96 | ( 0.61, 1.53) | 0.96 | ( 0.57, 1.60) | 0.00 | (-0.05, 0.04) | |
| >=65 | 1670 | 183 | 11.0 | 1739 | 147 | 8.5 | 0.0134 | 0.77 | ( 0.63, 0.95) | 0.75 | ( 0.60, 0.94) | -0.03 | (-0.04,-0.01) | |
| Region | | | | | | | | | | | | | | 0.4478 |
| North America | 273 | 61 | 22.3 | 273 | 50 | 18.3 | 0.2421 | 0.82 | ( 0.59, 1.14) | 0.78 | ( 0.51, 1.18) | -0.04 | (-0.11, 0.03) | |
| Latin America | 511 | 51 | 10.0 | 504 | 47 | 9.3 | 0.7239 | 0.93 | ( 0.64, 1.36) | 0.93 | ( 0.61, 1.41) | -0.01 | (-0.04, 0.03) | |
| Europe | 865 | 75 | 8.7 | 894 | 49 | 5.5 | 0.0090 | 0.63 | ( 0.45, 0.89) | 0.61 | ( 0.42, 0.89) | -0.03 | (-0.06,-0.01) | |
| Asia | 231 | 14 | 6.1 | 248 | 12 | 4.8 | 0.5553 | 0.80 | ( 0.38, 1.69) | 0.79 | ( 0.36, 1.74) | -0.01 | (-0.05, 0.03) | |
| Other | 121 | 16 | 13.2 | 133 | 20 | 15.0 | 0.6788 | 1.14 | ( 0.62, 2.09) | 1.16 | ( 0.57, 2.36) | 0.02 | (-0.07, 0.10) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7801 |
| Diabetic | 1045 | 134 | 12.8 | 1081 | 113 | 10.5 | 0.0883 | 0.82 | ( 0.64, 1.03) | 0.79 | ( 0.61, 1.04) | -0.02 | (-0.05, 0.00) | |
| Non-Diabetic | 956 | 83 | 8.7 | 971 | 65 | 6.7 | 0.1013 | 0.77 | ( 0.56, 1.05) | 0.75 | ( 0.54, 1.06) | -0.02 | (-0.04, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0560 |
| <30 | 1086 | 111 | 10.2 | 1094 | 73 | 6.7 | 0.0029 | 0.65 | ( 0.49, 0.87) | 0.63 | ( 0.46, 0.85) | -0.04 | (-0.06,-0.01) | |
| >=30 | 915 | 106 | 11.6 | 958 | 105 | 11.0 | 0.6692 | 0.95 | ( 0.73, 1.22) | 0.94 | ( 0.71, 1.25) | -0.01 | (-0.03, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3030 |
| <130 | 827 | 90 | 10.9 | 853 | 83 | 9.7 | 0.4372 | 0.89 | ( 0.67, 1.19) | 0.88 | ( 0.64, 1.21) | -0.01 | (-0.04, 0.02) | |
| >=130 | 1174 | 127 | 10.8 | 1199 | 95 | 7.9 | 0.0155 | 0.73 | ( 0.57, 0.94) | 0.71 | ( 0.54, 0.94) | -0.03 | (-0.05,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9757 |
| <75 | 935 | 119 | 12.7 | 934 | 94 | 10.1 | 0.0701 | 0.79 | ( 0.61, 1.02) | 0.77 | ( 0.58, 1.02) | -0.03 | (-0.06, 0.00) | |
| 75 to <85 | 657 | 64 | 9.7 | 703 | 55 | 7.8 | 0.2111 | 0.80 | ( 0.57, 1.13) | 0.79 | ( 0.54, 1.15) | -0.02 | (-0.05, 0.01) | |
| >=85 | 409 | 34 | 8.3 | 415 | 29 | 7.0 | 0.4742 | 0.84 | ( 0.52, 1.35) | 0.83 | ( 0.49, 1.39) | -0.01 | (-0.05, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.9281 |
| <30 | 161 | 48 | 29.8 | 148 | 38 | 25.7 | 0.4175 | 0.86 ( 0.60, 1.24) | 0.81 ( 0.49, 1.34) | -0.04 (-0.14, 0.06) | |
| 30 to <45 | 550 | 70 | 12.7 | 564 | 59 | 10.5 | 0.2373 | 0.82 ( 0.59, 1.14) | 0.80 ( 0.55, 1.16) | -0.02 (-0.06, 0.01) | |
| >=45 | 1289 | 99 | 7.7 | 1340 | 81 | 6.0 | 0.0969 | 0.79 ( 0.59, 1.05) | 0.77 ( 0.57, 1.05) | -0.02 (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.8332 |
| Normal (<30) | 764 | 66 | 8.6 | 787 | 53 | 6.7 | 0.1589 | 0.78 ( 0.55, 1.10) | 0.76 ( 0.52, 1.11) | -0.02 (-0.05, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 99 | 10.7 | 938 | 78 | 8.3 | 0.0739 | 0.77 ( 0.58, 1.03) | 0.75 ( 0.55, 1.03) | -0.02 (-0.05, 0.00) | |
| Macroalbuminuria (>300) | 311 | 52 | 16.7 | 318 | 47 | 14.8 | 0.5041 | 0.88 ( 0.62, 1.27) | 0.86 ( 0.56, 1.33) | -0.02 (-0.08, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.6210 |
| Low, moderate or high | 1477 | 117 | 7.9 | 1548 | 96 | 6.2 | 0.0646 | 0.78 ( 0.60, 1.02) | 0.77 ( 0.58, 1.02) | -0.02 (-0.04, 0.00) | |
| Very high | 519 | 100 | 19.3 | 495 | 82 | 16.6 | 0.2624 | 0.86 ( 0.66, 1.12) | 0.83 ( 0.60, 1.15) | -0.03 (-0.07, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.9615 |
| No | 411 | 53 | 12.9 | 410 | 42 | 10.2 | 0.2350 | 0.79 ( 0.54, 1.16) | 0.77 ( 0.50, 1.19) | -0.03 (-0.07, 0.02) | |
| Yes | 1590 | 164 | 10.3 | 1642 | 136 | 8.3 | 0.0466 | 0.80 ( 0.65, <1.00) | 0.79 ( 0.62, 1.00) | -0.02 (-0.04, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.2558 |
| No | 282 | 31 | 11.0 | 277 | 18 | 6.5 | 0.0603 | 0.59 ( 0.34, 1.03) | 0.56 ( 0.31, 1.03) | -0.04 (-0.09, 0.00) | |
| Yes | 1719 | 186 | 10.8 | 1775 | 160 | 9.0 | 0.0740 | 0.83 ( 0.68, 1.02) | 0.82 ( 0.65, 1.02) | -0.02 (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.2859 |
| No | 229 | 17 | 7.4 | 250 | 10 | 4.0 | 0.1046 | 0.54 ( 0.25, 1.15) | 0.52 ( 0.23, 1.16) | -0.03 (-0.08, 0.01) | |
| Yes | 1772 | 200 | 11.3 | 1802 | 168 | 9.3 | 0.0534 | 0.83 ( 0.68, >1.00) | 0.81 ( 0.65, 1.00) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 159 | 7.9 | 2052 | 179 | 8.7 | 0.3709 | 1.10 ( 0.89, 1.35) | 1.11 ( 0.89, 1.38) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 145 | 7.2 | 2052 | 118 | 5.8 | 0.0533 | 0.79 ( 0.63, >1.00) | 0.78 ( 0.61, 1.00) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 144 | 7.2 | 2052 | 129 | 6.3 | 0.2479 | 0.87 | ( 0.69, 1.10) | 0.87 | ( 0.68, 1.11) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 122 | 6.1 | 2052 | 136 | 6.6 | 0.4890 | 1.09 | ( 0.86, 1.38) | 1.09 | ( 0.85, 1.41) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 117 | 5.8 | 2052 | 134 | 6.5 | 0.3670 | 1.12 | ( 0.88, 1.42) | 1.12 | ( 0.87, 1.45) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 121 | 6.0 | 2052 | 104 | 5.1 | 0.1737 | 0.84 | ( 0.65, 1.08) | 0.83 | ( 0.63, 1.09) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 101 | 5.0 | 2052 | 124 | 6.0 | 0.1665 | 1.20 ( 0.93, 1.55) | 1.21 ( 0.92, 1.59) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 115 | 5.7 | 2052 | 87 | 4.2 | 0.0275 | 0.74 | ( 0.56, 0.97) | 0.73 | ( 0.55, 0.97) | -0.02 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.9756 |
| Male | 1065 | 61 | 5.7 | 1093 | 46 | 4.2 | 0.1041 | 0.73 | ( 0.51, 1.07) | 0.72 | ( 0.49, 1.07) | -0.02 | (-0.03, 0.00) | |
| Female | 936 | 54 | 5.8 | 959 | 41 | 4.3 | 0.1362 | 0.74 | ( 0.50, 1.10) | 0.73 | ( 0.48, 1.11) | -0.01 | (-0.03, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.6460 |
| <65 | 331 | 24 | 7.3 | 313 | 19 | 6.1 | 0.5486 | 0.84 | ( 0.47, 1.50) | 0.83 | ( 0.44, 1.54) | -0.01 | (-0.05, 0.03) | |
| >=65 | 1670 | 91 | 5.4 | 1739 | 68 | 3.9 | 0.0332 | 0.72 | ( 0.53, 0.98) | 0.71 | ( 0.51, 0.97) | -0.02 | (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | | 0.0731 |
| North America | 273 | 23 | 8.4 | 273 | 25 | 9.2 | 0.7624 | 1.09 | ( 0.63, 1.87) | 1.10 | ( 0.61, 1.98) | 0.01 | (-0.04, 0.05) | |
| Latin America | 511 | 35 | 6.8 | 504 | 26 | 5.2 | 0.2572 | 0.75 | ( 0.46, 1.23) | 0.74 | ( 0.44, 1.25) | -0.02 | (-0.05, 0.01) | |
| Europe | 865 | 36 | 4.2 | 894 | 16 | 1.8 | 0.0033 | 0.43 | ( 0.24, 0.77) | 0.42 | ( 0.23, 0.76) | -0.02 | (-0.04,-0.01) | |
| Asia | 231 | 13 | 5.6 | 248 | 7 | 2.8 | 0.1251 | 0.50 | ( 0.20, 1.24) | 0.49 | ( 0.19, 1.24) | -0.03 | (-0.06, 0.01) | |
| Other | 121 | 8 | 6.6 | 133 | 13 | 9.8 | 0.3606 | 1.48 | ( 0.63, 3.44) | 1.53 | ( 0.61, 3.83) | 0.03 | (-0.04, 0.10) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9838 |
| Diabetic | 1045 | 83 | 7.9 | 1081 | 63 | 5.8 | 0.0539 | 0.73 | ( 0.53, 1.01) | 0.72 | ( 0.51, 1.01) | -0.02 | (-0.04, 0.00) | |
| Non-Diabetic | 956 | 32 | 3.3 | 971 | 24 | 2.5 | 0.2526 | 0.74 | ( 0.44, 1.24) | 0.73 | ( 0.43, 1.25) | -0.01 | (-0.02, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1686 |
| <30 | 1086 | 61 | 5.6 | 1094 | 37 | 3.4 | 0.0118 | 0.60 | ( 0.40, 0.90) | 0.59 | ( 0.39, 0.89) | -0.02 | (-0.04, 0.00) | |
| >=30 | 915 | 54 | 5.9 | 958 | 50 | 5.2 | 0.5191 | 0.88 | ( 0.61, 1.29) | 0.88 | ( 0.59, 1.30) | -0.01 | (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1639 |
| <130 | 827 | 53 | 6.4 | 853 | 32 | 3.8 | 0.0130 | 0.59 | ( 0.38, 0.90) | 0.57 | ( 0.36, 0.89) | -0.03 | (-0.05,-0.01) | |
| >=130 | 1174 | 62 | 5.3 | 1199 | 55 | 4.6 | 0.4350 | 0.87 | ( 0.61, 1.24) | 0.86 | ( 0.59, 1.25) | -0.01 | (-0.02, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8100 |
| <75 | 935 | 60 | 6.4 | 934 | 46 | 4.9 | 0.1632 | 0.77 | ( 0.53, 1.11) | 0.76 | ( 0.51, 1.12) | -0.01 | (-0.04, 0.01) | |
| 75 to <85 | 657 | 36 | 5.5 | 703 | 25 | 3.6 | 0.0868 | 0.65 | ( 0.39, 1.07) | 0.64 | ( 0.38, 1.07) | -0.02 | (-0.04, 0.00) | |
| >=85 | 409 | 19 | 4.6 | 415 | 16 | 3.9 | 0.5739 | 0.83 | ( 0.43, 1.59) | 0.82 | ( 0.42, 1.62) | -0.01 | (-0.04, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0852 |
| <30 | 161 | 12 | 7.5 | 148 | 17 | 11.5 | 0.2246 | 1.54 ( 0.76, 3.12) | 1.61 ( 0.74, 3.50) | 0.04 (-0.03, 0.11) | |
| 30 to <45 | 550 | 40 | 7.3 | 564 | 25 | 4.4 | 0.0432 | 0.61 ( 0.37, 0.99) | 0.59 ( 0.35, 0.99) | -0.03 (-0.06, 0.00) | |
| >=45 | 1289 | 63 | 4.9 | 1340 | 45 | 3.4 | 0.0483 | 0.69 ( 0.47, <1.00) | 0.68 ( 0.46, 1.00) | -0.02 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.0850 |
| Normal (<30) | 764 | 40 | 5.2 | 787 | 19 | 2.4 | 0.0037 | 0.46 ( 0.27, 0.79) | 0.45 ( 0.26, 0.78) | -0.03 (-0.05,-0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 50 | 5.4 | 938 | 41 | 4.4 | 0.2905 | 0.81 ( 0.54, 1.20) | 0.80 ( 0.52, 1.22) | -0.01 (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 311 | 25 | 8.0 | 318 | 27 | 8.5 | 0.8369 | 1.06 ( 0.63, 1.78) | 1.06 ( 0.60, 1.87) | 0.00 (-0.04, 0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0765 |
| Low, moderate or high | 1477 | 72 | 4.9 | 1548 | 46 | 3.0 | 0.0069 | 0.61 ( 0.42, 0.88) | 0.60 ( 0.41, 0.87) | -0.02 (-0.03,-0.01) | |
| Very high | 519 | 43 | 8.3 | 495 | 41 | 8.3 | 0.9989 | 1.00 ( 0.66, 1.51) | 1.00 ( 0.64, 1.56) | 0.00 (-0.03, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.9826 |
| No | 411 | 27 | 6.6 | 410 | 20 | 4.9 | 0.2969 | 0.74 ( 0.42, 1.30) | 0.73 ( 0.40, 1.32) | -0.02 (-0.05, 0.01) | |
| Yes | 1590 | 88 | 5.5 | 1642 | 67 | 4.1 | 0.0531 | 0.74 ( 0.54, 1.01) | 0.73 ( 0.52, 1.01) | -0.01 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.4365 |
| No | 282 | 10 | 3.5 | 277 | 10 | 3.6 | 0.9675 | 1.02 ( 0.43, 2.41) | 1.02 ( 0.42, 2.49) | 0.00 (-0.03, 0.03) | |
| Yes | 1719 | 105 | 6.1 | 1775 | 77 | 4.3 | 0.0186 | 0.71 ( 0.53, 0.95) | 0.70 ( 0.52, 0.94) | -0.02 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9724 |
| No | 229 | 11 | 4.8 | 250 | 9 | 3.6 | 0.5107 | 0.75 ( 0.32, 1.78) | 0.74 ( 0.30, 1.82) | -0.01 (-0.05, 0.02) | |
| Yes | 1772 | 104 | 5.9 | 1802 | 78 | 4.3 | 0.0362 | 0.74 ( 0.55, 0.98) | 0.73 ( 0.54, 0.98) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 62 | 3.1 | 2052 | 35 | 1.7 | 0.0037 | 0.55 | ( 0.37, 0.83) | 0.54 | ( 0.36, 0.83) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4235 |
| Male | 1065 | 32 | 3.0 | 1093 | 21 | 1.9 | 0.1040 | 0.64 | ( 0.37, 1.10) | 0.63 | ( 0.36, 1.10) | -0.01 | (-0.02, 0.00) | |
| Female | 936 | 30 | 3.2 | 959 | 14 | 1.5 | 0.0117 | 0.46 | ( 0.24, 0.85) | 0.45 | ( 0.24, 0.85) | -0.02 | (-0.03, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.1590 |
| <65 | 331 | 8 | 2.4 | 313 | 1 | 0.3 | 0.0234 | 0.13 | ( 0.02, 1.05) | 0.13 | ( 0.02, 1.04) | -0.02 | (-0.04, 0.00) | |
| >=65 | 1670 | 54 | 3.2 | 1739 | 34 | 2.0 | 0.0186 | 0.60 | ( 0.40, 0.92) | 0.60 | ( 0.39, 0.92) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | 0.5891 |
| North America | 273 | 13 | 4.8 | 273 | 9 | 3.3 | 0.3840 | 0.69 | ( 0.30, 1.59) | 0.68 | ( 0.29, 1.62) | -0.01 | (-0.05, 0.02) | |
| Latin America | 511 | 9 | 1.8 | 504 | 5 | 1.0 | 0.2935 | 0.56 | ( 0.19, 1.67) | 0.56 | ( 0.19, 1.68) | -0.01 | (-0.02, 0.01) | |
| Europe | 865 | 29 | 3.4 | 894 | 14 | 1.6 | 0.0153 | 0.47 | ( 0.25, 0.88) | 0.46 | ( 0.24, 0.87) | -0.02 | (-0.03, 0.00) | |
| Asia | 231 | 7 | 3.0 | 248 | 7 | 2.8 | 0.8927 | 0.93 | ( 0.33, 2.61) | 0.93 | ( 0.32, 2.69) | 0.00 | (-0.03, 0.03) | |
| Other | 121 | 4 | 3.3 | 133 | 0 | 0 | 0.0556 | 0.10 | (<0.01, 1.86) | 0.10 | (<0.01, 1.84) | -0.03 | (-0.07, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2104 |
| Diabetic | 1045 | 27 | 2.6 | 1081 | 20 | 1.9 | 0.2501 | 0.72 | ( 0.40, 1.27) | 0.71 | ( 0.40, 1.28) | -0.01 | (-0.02, 0.01) | |
| Non-Diabetic | 956 | 35 | 3.7 | 971 | 15 | 1.5 | 0.0035 | 0.42 | ( 0.23, 0.77) | 0.41 | ( 0.22, 0.76) | -0.02 | (-0.04,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4953 |
| <30 | 1086 | 37 | 3.4 | 1094 | 23 | 2.1 | 0.0627 | 0.62 | ( 0.37, 1.03) | 0.61 | ( 0.36, 1.03) | -0.01 | (-0.03, 0.00) | |
| >=30 | 915 | 25 | 2.7 | 958 | 12 | 1.3 | 0.0214 | 0.46 | ( 0.23, 0.91) | 0.45 | ( 0.23, 0.90) | -0.01 | (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6645 |
| <130 | 827 | 31 | 3.7 | 853 | 16 | 1.9 | 0.0200 | 0.50 | ( 0.28, 0.91) | 0.49 | ( 0.27, 0.90) | -0.02 | (-0.03, 0.00) | |
| >=130 | 1174 | 31 | 2.6 | 1199 | 19 | 1.6 | 0.0734 | 0.60 | ( 0.34, 1.06) | 0.59 | ( 0.33, 1.06) | -0.01 | (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3488 |
| <75 | 935 | 34 | 3.6 | 934 | 17 | 1.8 | 0.0160 | 0.50 | ( 0.28, 0.89) | 0.49 | ( 0.27, 0.89) | -0.02 | (-0.03, 0.00) | |
| 75 to <85 | 657 | 16 | 2.4 | 703 | 14 | 2.0 | 0.5776 | 0.82 | ( 0.40, 1.66) | 0.81 | ( 0.39, 1.68) | 0.00 | (-0.02, 0.01) | |
| >=85 | 409 | 12 | 2.9 | 415 | 4 | 1.0 | 0.0404 | 0.33 | ( 0.11, 1.01) | 0.32 | ( 0.10, 1.01) | -0.02 | (-0.04, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4610 |
| <30 | 161 | 10 | 6.2 | 148 | 7 | 4.7 | 0.5683 | 0.76 | ( 0.30, 1.95) | 0.75 | ( 0.28, 2.02) | -0.01 | (-0.07, 0.04) | |
| 30 to <45 | 550 | 20 | 3.6 | 564 | 14 | 2.5 | 0.2629 | 0.68 | ( 0.35, 1.34) | 0.67 | ( 0.34, 1.35) | -0.01 | (-0.03, 0.01) | |
| >=45 | 1289 | 32 | 2.5 | 1340 | 14 | 1.0 | 0.0049 | 0.42 | ( 0.23, 0.78) | 0.41 | ( 0.22, 0.78) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4450 |
| Normal (<30) | 764 | 20 | 2.6 | 787 | 12 | 1.5 | 0.1300 | 0.58 | ( 0.29, 1.18) | 0.58 | ( 0.28, 1.19) | -0.01 | (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 30 | 3.3 | 938 | 20 | 2.1 | 0.1338 | 0.65 | ( 0.37, 1.14) | 0.65 | ( 0.36, 1.15) | -0.01 | (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 311 | 11 | 3.5 | 318 | 3 | 0.9 | 0.0275 | 0.27 | ( 0.08, 0.95) | 0.26 | ( 0.07, 0.94) | -0.03 | (-0.05, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2869 |
| Low, moderate or high | 1477 | 39 | 2.6 | 1548 | 19 | 1.2 | 0.0046 | 0.46 | ( 0.27, 0.80) | 0.46 | ( 0.26, 0.80) | -0.01 | (-0.02, 0.00) | |
| Very high | 519 | 23 | 4.4 | 495 | 16 | 3.2 | 0.3209 | 0.73 | ( 0.39, 1.36) | 0.72 | ( 0.38, 1.38) | -0.01 | (-0.04, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4988 |
| No | 411 | 16 | 3.9 | 410 | 11 | 2.7 | 0.3310 | 0.69 | ( 0.32, 1.47) | 0.68 | ( 0.31, 1.48) | -0.01 | (-0.04, 0.01) | |
| Yes | 1590 | 46 | 2.9 | 1642 | 24 | 1.5 | 0.0052 | 0.51 | ( 0.31, 0.82) | 0.50 | ( 0.30, 0.82) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8622 |
| No | 282 | 12 | 4.3 | 277 | 7 | 2.5 | 0.2595 | 0.59 | ( 0.24, 1.49) | 0.58 | ( 0.23, 1.50) | -0.02 | (-0.05, 0.01) | |
| Yes | 1719 | 50 | 2.9 | 1775 | 28 | 1.6 | 0.0077 | 0.54 | ( 0.34, 0.86) | 0.53 | ( 0.34, 0.85) | -0.01 | (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.7807 |
| No | 229 | 6 | 2.6 | 250 | 3 | 1.2 | 0.2529 | 0.46 | ( 0.12, 1.81) | 0.45 | ( 0.11, 1.83) | -0.01 | (-0.04, 0.01) | |
| Yes | 1772 | 56 | 3.2 | 1802 | 32 | 1.8 | 0.0076 | 0.56 | ( 0.37, 0.86) | 0.55 | ( 0.36, 0.86) | -0.01 | (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 52 | 2.6 | 2052 | 46 | 2.2 | 0.4595 | 0.86 ( 0.58, 1.28) | 0.86 ( 0.58, 1.28) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 47 | 2.3 | 2052 | 43 | 2.1 | 0.5843 | 0.89 ( 0.59, 1.34) | 0.89 ( 0.59, 1.35) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 33 | 1.6 | 2052 | 37 | 1.8 | 0.7068 | 1.09 ( 0.69, 1.74) | 1.10 ( 0.68, 1.76) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 22 | 1.1 | 2052 | 25 | 1.2 | 0.7238 | 1.11 ( 0.63, 1.96) | 1.11 ( 0.62, 1.97) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 24 | 1.2 | 2052 | 15 | 0.7 | 0.1267 | 0.61 ( 0.32, 1.16) | 0.61 ( 0.32, 1.16) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 362 | 18.1 | 2052 | 304 | 14.8 | 0.0049 | 0.82 | ( 0.71, 0.94) | 0.79 | ( 0.67, 0.93) | -0.03 | (-0.06,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.3720 |
| Male | 1065 | 198 | 18.6 | 1093 | 176 | 16.1 | 0.1267 | 0.87 | ( 0.72, 1.04) | 0.84 | ( 0.67, 1.05) | -0.02 | (-0.06, 0.01) | |
| Female | 936 | 164 | 17.5 | 959 | 128 | 13.3 | 0.0119 | 0.76 | ( 0.62, 0.94) | 0.73 | ( 0.56, 0.93) | -0.04 | (-0.07,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.8251 |
| <65 | 331 | 59 | 17.8 | 313 | 44 | 14.1 | 0.1924 | 0.79 | ( 0.55, 1.13) | 0.75 | ( 0.49, 1.15) | -0.04 | (-0.09, 0.02) | |
| >=65 | 1670 | 303 | 18.1 | 1739 | 260 | 15.0 | 0.0121 | 0.82 | ( 0.71, 0.96) | 0.79 | ( 0.66, 0.95) | -0.03 | (-0.06,-0.01) | |
| Region | | | | | | | | | | | | | | 0.9879 |
| North America | 273 | 71 | 26.0 | 273 | 59 | 21.6 | 0.2279 | 0.83 | ( 0.61, 1.12) | 0.78 | ( 0.53, 1.16) | -0.04 | (-0.12, 0.03) | |
| Latin America | 511 | 103 | 20.2 | 504 | 84 | 16.7 | 0.1516 | 0.83 | ( 0.64, 1.07) | 0.79 | ( 0.58, 1.09) | -0.03 | (-0.08, 0.01) | |
| Europe | 865 | 131 | 15.1 | 894 | 107 | 12.0 | 0.0516 | 0.79 | ( 0.62, >1.00) | 0.76 | ( 0.58, 1.00) | -0.03 | (-0.06, 0.00) | |
| Asia | 231 | 38 | 16.5 | 248 | 37 | 14.9 | 0.6450 | 0.91 | ( 0.60, 1.37) | 0.89 | ( 0.54, 1.46) | -0.02 | (-0.08, 0.05) | |
| Other | 121 | 19 | 15.7 | 133 | 17 | 12.8 | 0.5051 | 0.81 | ( 0.44, 1.49) | 0.79 | ( 0.39, 1.59) | -0.03 | (-0.12, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0961 |
| Diabetic | 1045 | 222 | 21.2 | 1081 | 170 | 15.7 | 0.0010 | 0.74 | ( 0.62, 0.89) | 0.69 | ( 0.55, 0.86) | -0.06 | (-0.09,-0.02) | |
| Non-Diabetic | 956 | 140 | 14.6 | 971 | 134 | 13.8 | 0.5958 | 0.94 | ( 0.76, 1.17) | 0.93 | ( 0.72, 1.21) | -0.01 | (-0.04, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5939 |
| <30 | 1086 | 205 | 18.9 | 1094 | 175 | 16.0 | 0.0763 | 0.85 | ( 0.71, 1.02) | 0.82 | ( 0.66, 1.02) | -0.03 | (-0.06, 0.00) | |
| >=30 | 915 | 157 | 17.2 | 958 | 129 | 13.5 | 0.0263 | 0.78 | ( 0.63, 0.97) | 0.75 | ( 0.58, 0.97) | -0.04 | (-0.07, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4295 |
| <130 | 827 | 151 | 18.3 | 853 | 136 | 15.9 | 0.2075 | 0.87 | ( 0.71, 1.08) | 0.85 | ( 0.66, 1.10) | -0.02 | (-0.06, 0.01) | |
| >=130 | 1174 | 211 | 18.0 | 1199 | 168 | 14.0 | 0.0085 | 0.78 | ( 0.65, 0.94) | 0.74 | ( 0.60, 0.93) | -0.04 | (-0.07,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6473 |
| <75 | 935 | 188 | 20.1 | 934 | 146 | 15.6 | 0.0116 | 0.78 | ( 0.64, 0.95) | 0.74 | ( 0.58, 0.93) | -0.04 | (-0.08,-0.01) | |
| 75 to <85 | 657 | 115 | 17.5 | 703 | 102 | 14.5 | 0.1318 | 0.83 | ( 0.65, 1.06) | 0.80 | ( 0.60, 1.07) | -0.03 | (-0.07, 0.01) | |
| >=85 | 409 | 59 | 14.4 | 415 | 56 | 13.5 | 0.6997 | 0.94 | ( 0.67, 1.31) | 0.93 | ( 0.62, 1.37) | -0.01 | (-0.06, 0.04) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.5865 |
| <30 | 161 | 52 | 32.3 | 148 | 40 | 27.0 | 0.3114 | 0.84 ( 0.59, 1.18) | 0.78 ( 0.48, 1.27) | -0.05 (-0.15, 0.05) | |
| 30 to <45 | 550 | 109 | 19.8 | 564 | 102 | 18.1 | 0.4605 | 0.91 ( 0.72, 1.16) | 0.89 ( 0.66, 1.21) | -0.02 (-0.06, 0.03) | |
| >=45 | 1289 | 201 | 15.6 | 1340 | 162 | 12.1 | 0.0092 | 0.78 ( 0.64, 0.94) | 0.74 ( 0.60, 0.93) | -0.04 (-0.06,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.4228 |
| Normal (<30) | 764 | 123 | 16.1 | 787 | 106 | 13.5 | 0.1443 | 0.84 ( 0.66, 1.06) | 0.81 ( 0.61, 1.07) | -0.03 (-0.06, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 158 | 17.2 | 938 | 141 | 15.0 | 0.2128 | 0.88 ( 0.71, 1.08) | 0.85 ( 0.67, 1.09) | -0.02 (-0.05, 0.01) | |
| Macroalbuminuria (>300) | 311 | 81 | 26.0 | 318 | 57 | 17.9 | 0.0139 | 0.69 ( 0.51, 0.93) | 0.62 ( 0.42, 0.91) | -0.08 (-0.15,-0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8468 |
| Low, moderate or high | 1477 | 228 | 15.4 | 1548 | 200 | 12.9 | 0.0471 | 0.84 ( 0.70, <1.00) | 0.81 ( 0.66, 1.00) | -0.03 (-0.05, 0.00) | |
| Very high | 519 | 134 | 25.8 | 495 | 104 | 21.0 | 0.0709 | 0.81 ( 0.65, 1.02) | 0.76 ( 0.57, 1.02) | -0.05 (-0.10, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.2629 |
| No | 411 | 83 | 20.2 | 410 | 78 | 19.0 | 0.6728 | 0.94 ( 0.71, 1.24) | 0.93 ( 0.66, 1.31) | -0.01 (-0.07, 0.04) | |
| Yes | 1590 | 279 | 17.5 | 1642 | 226 | 13.8 | 0.0031 | 0.78 ( 0.67, 0.92) | 0.75 ( 0.62, 0.91) | -0.04 (-0.06,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.5184 |
| No | 282 | 50 | 17.7 | 277 | 45 | 16.2 | 0.6402 | 0.92 ( 0.63, 1.32) | 0.90 ( 0.58, 1.40) | -0.01 (-0.08, 0.05) | |
| Yes | 1719 | 312 | 18.2 | 1775 | 259 | 14.6 | 0.0045 | 0.80 ( 0.69, 0.93) | 0.77 ( 0.64, 0.92) | -0.04 (-0.06,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.7627 |
| No | 229 | 28 | 12.2 | 250 | 27 | 10.8 | 0.6246 | 0.88 ( 0.54, 1.45) | 0.87 ( 0.50, 1.52) | -0.01 (-0.07, 0.04) | |
| Yes | 1772 | 334 | 18.8 | 1802 | 277 | 15.4 | 0.0058 | 0.82 ( 0.71, 0.94) | 0.78 ( 0.66, 0.93) | -0.03 (-0.06,-0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 185 | 9.2 | 2052 | 202 | 9.8 | 0.5167 | 1.06 ( 0.88, 1.29) | 1.07 ( 0.87, 1.32) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 120 | 6.0 | 2052 | 95 | 4.6 | 0.0522 | 0.77 ( 0.59, >1.00) | 0.76 ( 0.58, 1.00) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 98 | 4.9 | 2052 | 116 | 5.7 | 0.2823 | 1.15 | ( 0.89, 1.50) | 1.16 | ( 0.88, 1.53) | 0.01 | (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 82 | 4.1 | 2052 | 90 | 4.4 | 0.6493 | 1.07 ( 0.80, 1.43) | 1.07 ( 0.79, 1.46) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 79 | 3.9 | 2052 | 65 | 3.2 | 0.1797 | 0.80 | ( 0.58, 1.11) | 0.80 | ( 0.57, 1.11) | -0.01 | (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 53 | 2.6 | 2052 | 70 | 3.4 | 0.1571 | 1.29 | ( 0.91, 1.83) | 1.30 | ( 0.90, 1.86) | 0.01 | ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 67 | 3.3 | 2052 | 67 | 3.3 | 0.8822 | 0.98 ( 0.70, 1.36) | 0.97 ( 0.69, 1.37) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 40 | 2.0 | 2052 | 68 | 3.3 | 0.0094 | 1.66 ( 1.13, 2.44) | 1.68 ( 1.13, 2.50) | 0.01 ( 0.00, 0.02) | |
| Sex | | | | | | | | | | | 0.1663 |
| Male | 1065 | 26 | 2.4 | 1093 | 35 | 3.2 | 0.2863 | 1.31 ( 0.80, 2.16) | 1.32 ( 0.79, 2.21) | 0.01 (-0.01, 0.02) | |
| Female | 936 | 14 | 1.5 | 959 | 33 | 3.4 | 0.0065 | 2.30 ( 1.24, 4.27) | 2.35 ( 1.25, 4.41) | 0.02 ( 0.01, 0.03) | |
| Age [years] | | | | | | | | | | | 0.7306 |
| <65 | 331 | 4 | 1.2 | 313 | 5 | 1.6 | 0.6743 | 1.32 ( 0.36, 4.88) | 1.33 ( 0.35, 4.99) | 0.00 (-0.01, 0.02) | |
| >=65 | 1670 | 36 | 2.2 | 1739 | 63 | 3.6 | 0.0108 | 1.68 ( 1.12, 2.52) | 1.71 ( 1.13, 2.58) | 0.01 ( 0.00, 0.03) | |
| Region | | | | | | | | | | | 0.9208 |
| North America | 273 | 12 | 4.4 | 273 | 17 | 6.2 | 0.3400 | 1.42 ( 0.69, 2.91) | 1.44 ( 0.68, 3.08) | 0.02 (-0.02, 0.06) | |
| Latin America | 511 | 5 | 1.0 | 504 | 11 | 2.2 | 0.1236 | 2.23 ( 0.78, 6.37) | 2.26 ( 0.78, 6.55) | 0.01 ( 0.00, 0.03) | |
| Europe | 865 | 13 | 1.5 | 894 | 20 | 2.2 | 0.2565 | 1.49 ( 0.75, 2.97) | 1.50 ( 0.74, 3.03) | 0.01 (-0.01, 0.02) | |
| Asia | 231 | 4 | 1.7 | 248 | 6 | 2.4 | 0.5988 | 1.40 ( 0.40, 4.89) | 1.41 ( 0.39, 5.05) | 0.01 (-0.02, 0.03) | |
| Other | 121 | 6 | 5.0 | 133 | 14 | 10.5 | 0.0999 | 2.12 ( 0.84, 5.35) | 2.25 ( 0.84, 6.07) | 0.06 (-0.01, 0.12) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.2901 |
| Diabetic | 1045 | 18 | 1.7 | 1081 | 38 | 3.5 | 0.0099 | 2.04 ( 1.17, 3.55) | 2.08 ( 1.18, 3.67) | 0.02 ( 0.00, 0.03) | |
| Non-Diabetic | 956 | 22 | 2.3 | 971 | 30 | 3.1 | 0.2856 | 1.34 ( 0.78, 2.31) | 1.35 ( 0.78, 2.36) | 0.01 (-0.01, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.8045 |
| <30 | 1086 | 20 | 1.8 | 1094 | 35 | 3.2 | 0.0433 | 1.74 ( 1.01, 2.99) | 1.76 ( 1.01, 3.07) | 0.01 ( 0.00, 0.03) | |
| >=30 | 915 | 20 | 2.2 | 958 | 33 | 3.4 | 0.1005 | 1.58 ( 0.91, 2.73) | 1.60 ( 0.91, 2.80) | 0.01 ( 0.00, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.5271 |
| <130 | 827 | 18 | 2.2 | 853 | 35 | 4.1 | 0.0239 | 1.89 ( 1.08, 3.30) | 1.92 ( 1.08, 3.42) | 0.02 ( 0.00, 0.04) | |
| >=130 | 1174 | 22 | 1.9 | 1199 | 33 | 2.8 | 0.1551 | 1.47 ( 0.86, 2.50) | 1.48 ( 0.86, 2.56) | 0.01 ( 0.00, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.7206 |
| <75 | 935 | 26 | 2.8 | 934 | 38 | 4.1 | 0.1258 | 1.46 ( 0.90, 2.39) | 1.48 ( 0.89, 2.46) | 0.01 ( 0.00, 0.03) | |
| 75 to <85 | 657 | 10 | 1.5 | 703 | 22 | 3.1 | 0.0507 | 2.06 ( 0.98, 4.31) | 2.09 ( 0.98, 4.45) | 0.02 ( 0.00, 0.03) | |
| >=85 | 409 | 4 | 1.0 | 415 | 8 | 1.9 | 0.2552 | 1.97 ( 0.60, 6.49) | 1.99 ( 0.59, 6.66) | 0.01 (-0.01, 0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1580 |
| <30 | 161 | 2 | 1.2 | 148 | 11 | 7.4 | 0.0068 | 5.98 | ( 1.35, 26.55) | 6.38 | ( 1.39, 29.30) | 0.06 | ( 0.02, 0.11) | |
| 30 to <45 | 550 | 16 | 2.9 | 564 | 20 | 3.5 | 0.5478 | 1.22 | ( 0.64, 2.33) | 1.23 | ( 0.63, 2.39) | 0.01 | (-0.01, 0.03) | |
| >=45 | 1289 | 22 | 1.7 | 1340 | 37 | 2.8 | 0.0680 | 1.62 | ( 0.96, 2.73) | 1.64 | ( 0.96, 2.79) | 0.01 | ( 0.00, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6555 |
| Normal (<30) | 764 | 15 | 2.0 | 787 | 23 | 2.9 | 0.2219 | 1.49 | ( 0.78, 2.83) | 1.50 | ( 0.78, 2.90) | 0.01 | (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 921 | 21 | 2.3 | 938 | 36 | 3.8 | 0.0514 | 1.68 | ( 0.99, 2.86) | 1.71 | ( 0.99, 2.95) | 0.02 | ( 0.00, 0.03) | |
| Macroalbuminuria (>300) | 311 | 3 | 1.0 | 318 | 9 | 2.8 | 0.0873 | 2.93 | ( 0.80, 10.74) | 2.99 | ( 0.80, 11.15) | 0.02 | ( 0.00, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4802 |
| Low, moderate or high | 1477 | 27 | 1.8 | 1548 | 44 | 2.8 | 0.0655 | 1.55 | ( 0.97, 2.50) | 1.57 | ( 0.97, 2.55) | 0.01 | ( 0.00, 0.02) | |
| Very high | 519 | 12 | 2.3 | 495 | 24 | 4.8 | 0.0291 | 2.10 | ( 1.06, 4.15) | 2.15 | ( 1.06, 4.35) | 0.03 | ( 0.00, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6180 |
| No | 411 | 12 | 2.9 | 410 | 23 | 5.6 | 0.0564 | 1.92 | ( 0.97, 3.81) | 1.98 | ( 0.97, 4.03) | 0.03 | ( 0.00, 0.05) | |
| Yes | 1590 | 28 | 1.8 | 1642 | 45 | 2.7 | 0.0610 | 1.56 | ( 0.98, 2.48) | 1.57 | ( 0.98, 2.53) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5323 |
| No | 282 | 8 | 2.8 | 277 | 10 | 3.6 | 0.6046 | 1.27 | ( 0.51, 3.18) | 1.28 | ( 0.50, 3.30) | 0.01 | (-0.02, 0.04) | |
| Yes | 1719 | 32 | 1.9 | 1775 | 58 | 3.3 | 0.0087 | 1.76 | ( 1.15, 2.69) | 1.78 | ( 1.15, 2.76) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3889 |
| No | 229 | 2 | 0.9 | 250 | 7 | 2.8 | 0.1208 | 3.21 | ( 0.67, 15.28) | 3.27 | ( 0.67, 15.90) | 0.02 | ( 0.00, 0.04) | |
| Yes | 1772 | 38 | 2.1 | 1802 | 61 | 3.4 | 0.0238 | 1.58 | ( 1.06, 2.35) | 1.60 | ( 1.06, 2.41) | 0.01 | ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 48 | 2.4 | 2052 | 57 | 2.8 | 0.4477 | 1.16 | ( 0.79, 1.69) | 1.16 | ( 0.79, 1.72) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 55 | 2.7 | 2052 | 48 | 2.3 | 0.4076 | 0.85 ( 0.58, 1.25) | 0.85 ( 0.57, 1.25) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 36 | 1.8 | 2052 | 21 | 1.0 | 0.0360 | 0.57 | ( 0.33, | 0.97) | 0.56 | ( 0.33, | 0.97) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.6399 |
| Male | 1065 | 20 | 1.9 | 1093 | 13 | 1.2 | 0.1925 | 0.63 | ( 0.32, | 1.27) | 0.63 | ( 0.31, | 1.27) | -0.01 | (-0.02, 0.00) | |
| Female | 936 | 16 | 1.7 | 959 | 8 | 0.8 | 0.0885 | 0.49 | ( 0.21, | 1.13) | 0.48 | ( 0.21, | 1.14) | -0.01 | (-0.02, 0.00) | |
| Age [years] | | | | | | | | | | | | | | | | 0.2028 |
| <65 | 331 | 5 | 1.5 | 313 | 0 | 0 | 0.0474 | 0.10 | (<0.01, | 1.73) | 0.09 | (<0.01, | 1.72) | -0.01 | (-0.03, 0.00) | |
| >=65 | 1670 | 31 | 1.9 | 1739 | 21 | 1.2 | 0.1224 | 0.65 | ( 0.38, | 1.13) | 0.65 | ( 0.37, | 1.13) | -0.01 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | | | 0.7937 |
| North America | 273 | 8 | 2.9 | 273 | 4 | 1.5 | 0.2430 | 0.50 | ( 0.15, | 1.64) | 0.49 | ( 0.15, | 1.66) | -0.01 | (-0.04, 0.01) | |
| Latin America | 511 | 7 | 1.4 | 504 | 5 | 1.0 | 0.5777 | 0.72 | ( 0.23, | 2.27) | 0.72 | ( 0.23, | 2.29) | 0.00 | (-0.02, 0.01) | |
| Europe | 865 | 13 | 1.5 | 894 | 8 | 0.9 | 0.2405 | 0.60 | ( 0.25, | 1.43) | 0.59 | ( 0.24, | 1.43) | -0.01 | (-0.02, 0.00) | |
| Asia | 231 | 3 | 1.3 | 248 | 3 | 1.2 | 0.9302 | 0.93 | ( 0.19, | 4.57) | 0.93 | ( 0.19, | 4.66) | 0.00 | (-0.02, 0.02) | |
| Other | 121 | 5 | 4.1 | 133 | 1 | 0.8 | 0.0764 | 0.18 | ( 0.02, | 1.54) | 0.18 | ( 0.02, | 1.53) | -0.03 | (-0.07, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | | 0.0659 |
| Diabetic | 1045 | 13 | 1.2 | 1081 | 13 | 1.2 | 0.9308 | 0.97 | ( 0.45, | 2.08) | 0.97 | ( 0.45, | 2.09) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 956 | 23 | 2.4 | 971 | 8 | 0.8 | 0.0058 | 0.34 | ( 0.15, | 0.76) | 0.34 | ( 0.15, | 0.76) | -0.02 | (-0.03, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.6047 |
| <30 | 1086 | 25 | 2.3 | 1094 | 13 | 1.2 | 0.0470 | 0.52 | ( 0.27, | >1.00) | 0.51 | ( 0.26, | 1.00) | -0.01 | (-0.02, 0.00) | |
| >=30 | 915 | 11 | 1.2 | 958 | 8 | 0.8 | 0.4280 | 0.69 | ( 0.28, | 1.72) | 0.69 | ( 0.28, | 1.73) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.7345 |
| <130 | 827 | 17 | 2.1 | 853 | 9 | 1.1 | 0.0967 | 0.51 | ( 0.23, | 1.14) | 0.51 | ( 0.23, | 1.15) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1174 | 19 | 1.6 | 1199 | 12 | 1.0 | 0.1853 | 0.62 | ( 0.30, | 1.27) | 0.61 | ( 0.30, | 1.27) | -0.01 | (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.2412 |
| <75 | 935 | 20 | 2.1 | 934 | 10 | 1.1 | 0.0661 | 0.50 | ( 0.24, | 1.06) | 0.50 | ( 0.23, | 1.06) | -0.01 | (-0.02, 0.00) | |
| 75 to <85 | 657 | 8 | 1.2 | 703 | 9 | 1.3 | 0.9173 | 1.05 | ( 0.41, | 2.71) | 1.05 | ( 0.40, | 2.74) | 0.00 | (-0.01, 0.01) | |
| >=85 | 409 | 8 | 2.0 | 415 | 2 | 0.5 | 0.0533 | 0.25 | ( 0.05, | 1.15) | 0.24 | ( 0.05, | 1.15) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4778 |
| <30 | 161 | 8 | 5.0 | 148 | 7 | 4.7 | 0.9221 | 0.95 | ( 0.35, 2.56) | 0.95 | ( 0.34, 2.69) | 0.00 | (-0.05, 0.05) | |
| 30 to <45 | 550 | 10 | 1.8 | 564 | 6 | 1.1 | 0.2901 | 0.59 | ( 0.21, 1.60) | 0.58 | ( 0.21, 1.61) | -0.01 | (-0.02, 0.01) | |
| >=45 | 1289 | 18 | 1.4 | 1340 | 8 | 0.6 | 0.0384 | 0.43 | ( 0.19, 0.98) | 0.42 | ( 0.18, 0.98) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9541 |
| Normal (<30) | 764 | 11 | 1.4 | 787 | 7 | 0.9 | 0.3117 | 0.62 | ( 0.24, 1.59) | 0.61 | ( 0.24, 1.59) | -0.01 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 17 | 1.8 | 938 | 9 | 1.0 | 0.1037 | 0.52 | ( 0.23, 1.16) | 0.52 | ( 0.23, 1.16) | -0.01 | (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 311 | 8 | 2.6 | 318 | 5 | 1.6 | 0.3781 | 0.61 | ( 0.20, 1.85) | 0.61 | ( 0.20, 1.87) | -0.01 | (-0.03, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2434 |
| Low, moderate or high | 1477 | 22 | 1.5 | 1548 | 10 | 0.6 | 0.0234 | 0.43 | ( 0.21, 0.91) | 0.43 | ( 0.20, 0.91) | -0.01 | (-0.02, 0.00) | |
| Very high | 519 | 14 | 2.7 | 495 | 11 | 2.2 | 0.6257 | 0.82 | ( 0.38, 1.80) | 0.82 | ( 0.37, 1.82) | 0.00 | (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3148 |
| No | 411 | 11 | 2.7 | 410 | 9 | 2.2 | 0.6547 | 0.82 | ( 0.34, 1.96) | 0.82 | ( 0.33, 1.99) | 0.00 | (-0.03, 0.02) | |
| Yes | 1590 | 25 | 1.6 | 1642 | 12 | 0.7 | 0.0246 | 0.46 | ( 0.23, 0.92) | 0.46 | ( 0.23, 0.92) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8285 |
| No | 282 | 8 | 2.8 | 277 | 5 | 1.8 | 0.4183 | 0.64 | ( 0.21, 1.92) | 0.63 | ( 0.20, 1.95) | -0.01 | (-0.04, 0.01) | |
| Yes | 1719 | 28 | 1.6 | 1775 | 16 | 0.9 | 0.0539 | 0.55 | ( 0.30, 1.02) | 0.55 | ( 0.30, 1.02) | -0.01 | (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9611 |
| No | 229 | 5 | 2.2 | 250 | 3 | 1.2 | 0.4015 | 0.55 | ( 0.13, 2.27) | 0.54 | ( 0.13, 2.30) | -0.01 | (-0.03, 0.01) | |
| Yes | 1772 | 31 | 1.7 | 1802 | 18 | 1.0 | 0.0537 | 0.57 | ( 0.32, 1.02) | 0.57 | ( 0.32, 1.02) | -0.01 | (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 23 | 1.1 | 2052 | 28 | 1.4 | 0.5391 | 1.19 ( 0.69, 2.05) | 1.19 ( 0.68, 2.07) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 23 | 1.1 | 2052 | 19 | 0.9 | 0.4824 | 0.81 ( 0.44, 1.47) | 0.80 ( 0.44, 1.48) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.2.2.5**

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 158 | 7.9 | 2052 | 206 | 10.0 | 0.0170 | 1.27 | ( 1.04, 1.55) | 1.30 | ( 1.05, 1.62) | 0.02 | ( 0.00, 0.04) | |
| Sex | | | | | | | | | | | | | | 0.2678 |
| Male | 1065 | 59 | 5.5 | 1093 | 66 | 6.0 | 0.6201 | 1.09 | ( 0.78, 1.53) | 1.10 | ( 0.76, 1.57) | 0.00 | (-0.01, 0.02) | |
| Female | 936 | 99 | 10.6 | 959 | 140 | 14.6 | 0.0084 | 1.38 | ( 1.08, 1.76) | 1.45 | ( 1.10, 1.90) | 0.04 | ( 0.01, 0.07) | |
| Age [years] | | | | | | | | | | | | | | 0.0255 |
| <65 | 331 | 14 | 4.2 | 313 | 32 | 10.2 | 0.0032 | 2.42 | ( 1.32, 4.44) | 2.58 | ( 1.35, 4.93) | 0.06 | ( 0.02, 0.10) | |
| >=65 | 1670 | 144 | 8.6 | 1739 | 174 | 10.0 | 0.1651 | 1.16 | ( 0.94, 1.43) | 1.18 | ( 0.93, 1.49) | 0.01 | (-0.01, 0.03) | |
| Region | | | | | | | | | | | | | | 0.0223 |
| North America | 273 | 39 | 14.3 | 273 | 37 | 13.6 | 0.8047 | 0.95 | ( 0.63, 1.44) | 0.94 | ( 0.58, 1.53) | -0.01 | (-0.07, 0.05) | |
| Latin America | 511 | 38 | 7.4 | 504 | 69 | 13.7 | 0.0012 | 1.84 | ( 1.26, 2.68) | 1.97 | ( 1.30, 3.00) | 0.06 | ( 0.02, 0.10) | |
| Europe | 865 | 64 | 7.4 | 894 | 69 | 7.7 | 0.8001 | 1.04 | ( 0.75, 1.45) | 1.05 | ( 0.73, 1.49) | 0.00 | (-0.02, 0.03) | |
| Asia | 231 | 7 | 3.0 | 248 | 5 | 2.0 | 0.4779 | 0.67 | ( 0.21, 2.07) | 0.66 | ( 0.21, 2.10) | -0.01 | (-0.04, 0.02) | |
| Other | 121 | 10 | 8.3 | 133 | 26 | 19.5 | 0.0100 | 2.37 | ( 1.19, 4.70) | 2.70 | ( 1.24, 5.86) | 0.11 | ( 0.03, 0.20) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9881 |
| Diabetic | 1045 | 83 | 7.9 | 1081 | 109 | 10.1 | 0.0851 | 1.27 | ( 0.97, 1.67) | 1.30 | ( 0.96, 1.75) | 0.02 | ( 0.00, 0.05) | |
| Non-Diabetic | 956 | 75 | 7.8 | 971 | 97 | 10.0 | 0.0988 | 1.27 | ( 0.95, 1.70) | 1.30 | ( 0.95, 1.79) | 0.02 | ( 0.00, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2934 |
| <30 | 1086 | 82 | 7.6 | 1094 | 94 | 8.6 | 0.3720 | 1.14 | ( 0.86, 1.51) | 1.15 | ( 0.85, 1.57) | 0.01 | (-0.01, 0.03) | |
| >=30 | 915 | 76 | 8.3 | 958 | 112 | 11.7 | 0.0148 | 1.41 | ( 1.07, 1.86) | 1.46 | ( 1.08, 1.99) | 0.03 | ( 0.01, 0.06) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1853 |
| <130 | 827 | 59 | 7.1 | 853 | 91 | 10.7 | 0.0111 | 1.50 | ( 1.09, 2.05) | 1.55 | ( 1.10, 2.19) | 0.04 | ( 0.01, 0.06) | |
| >=130 | 1174 | 99 | 8.4 | 1199 | 115 | 9.6 | 0.3246 | 1.14 | ( 0.88, 1.47) | 1.15 | ( 0.87, 1.53) | 0.01 | (-0.01, 0.03) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6631 |
| <75 | 935 | 85 | 9.1 | 934 | 108 | 11.6 | 0.0791 | 1.27 | ( 0.97, 1.67) | 1.31 | ( 0.97, 1.76) | 0.02 | ( 0.00, 0.05) | |
| 75 to <85 | 657 | 50 | 7.6 | 703 | 62 | 8.8 | 0.4177 | 1.16 | ( 0.81, 1.66) | 1.17 | ( 0.80, 1.73) | 0.01 | (-0.02, 0.04) | |
| >=85 | 409 | 23 | 5.6 | 415 | 36 | 8.7 | 0.0894 | 1.54 | ( 0.93, 2.56) | 1.59 | ( 0.93, 2.74) | 0.03 | ( 0.00, 0.07) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.2418 |
| <30 | 161 | 20 | 12.4 | 148 | 20 | 13.5 | 0.7753 | 1.09 ( 0.61, | 1.94) | 1.10 ( 0.57, | 2.14) | 0.01 (-0.06, 0.09) | |
| 30 to <45 | 550 | 57 | 10.4 | 564 | 61 | 10.8 | 0.8064 | 1.04 ( 0.74, | 1.47) | 1.05 ( 0.72, | 1.54) | 0.00 (-0.03, 0.04) | |
| >=45 | 1289 | 81 | 6.3 | 1340 | 125 | 9.3 | 0.0037 | 1.48 ( 1.13, | 1.94) | 1.53 ( 1.15, | 2.05) | 0.03 ( 0.01, 0.05) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.6320 |
| Normal (<30) | 764 | 62 | 8.1 | 787 | 75 | 9.5 | 0.3263 | 1.17 ( 0.85, | 1.62) | 1.19 ( 0.84, | 1.70) | 0.01 (-0.01, 0.04) | |
| Microalbuminuria (30 to <=300) | 921 | 74 | 8.0 | 938 | 97 | 10.3 | 0.0854 | 1.29 ( 0.96, | 1.72) | 1.32 ( 0.96, | 1.81) | 0.02 ( 0.00, 0.05) | |
| Macroalbuminuria (>300) | 311 | 21 | 6.8 | 318 | 34 | 10.7 | 0.0803 | 1.58 ( 0.94, | 2.67) | 1.65 ( 0.94, | 2.92) | 0.04 ( 0.00, 0.08) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.4384 |
| Low, moderate or high | 1477 | 104 | 7.0 | 1548 | 148 | 9.6 | 0.0122 | 1.36 ( 1.07, | 1.73) | 1.40 ( 1.07, | 1.81) | 0.03 ( 0.01, 0.04) | |
| Very high | 519 | 53 | 10.2 | 495 | 58 | 11.7 | 0.4429 | 1.15 ( 0.81, | 1.63) | 1.17 ( 0.79, | 1.73) | 0.02 (-0.02, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.7291 |
| No | 411 | 37 | 9.0 | 410 | 50 | 12.2 | 0.1373 | 1.35 ( 0.91, | 2.03) | 1.40 ( 0.90, | 2.20) | 0.03 (-0.01, 0.07) | |
| Yes | 1590 | 121 | 7.6 | 1642 | 156 | 9.5 | 0.0549 | 1.25 ( 0.99, | 1.57) | 1.27 ( 0.99, | 1.63) | 0.02 ( 0.00, 0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.8056 |
| No | 282 | 23 | 8.2 | 277 | 27 | 9.7 | 0.5098 | 1.20 ( 0.70, | 2.03) | 1.22 ( 0.68, | 2.18) | 0.02 (-0.03, 0.06) | |
| Yes | 1719 | 135 | 7.9 | 1775 | 179 | 10.1 | 0.0211 | 1.28 ( 1.04, | 1.59) | 1.32 ( 1.04, | 1.66) | 0.02 ( 0.00, 0.04) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.5375 |
| No | 229 | 15 | 6.6 | 250 | 25 | 10.0 | 0.1728 | 1.53 ( 0.83, | 2.82) | 1.59 ( 0.81, | 3.09) | 0.03 (-0.01, 0.08) | |
| Yes | 1772 | 143 | 8.1 | 1802 | 181 | 10.0 | 0.0398 | 1.24 ( 1.01, | 1.53) | 1.27 ( 1.01, | 1.60) | 0.02 ( 0.00, 0.04) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 185 | 9.2 | 2052 | 165 | 8.0 | 0.1723 | 0.87 ( 0.71, 1.06) | 0.86 ( 0.69, 1.07) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Nasopharyngitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 87 | 4.3 | 2052 | 110 | 5.4 | 0.1339 | 1.23 ( 0.94, 1.62) | 1.25 ( 0.93, 1.66) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Upper respiratory tract infection

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 106 | 5.3 | 2052 | 78 | 3.8 | 0.0222 | 0.72 ( 0.54, 0.95) | 0.71 ( 0.52, 0.95) | -0.01 (-0.03, 0.00) | |
| Sex | | | | | | | | | | | 0.7365 |
| Male | 1065 | 49 | 4.6 | 1093 | 38 | 3.5 | 0.1843 | 0.76 ( 0.50, 1.14) | 0.75 ( 0.48, 1.15) | -0.01 (-0.03, 0.01) | |
| Female | 936 | 57 | 6.1 | 959 | 40 | 4.2 | 0.0581 | 0.68 ( 0.46, 1.02) | 0.67 ( 0.44, 1.02) | -0.02 (-0.04, 0.00) | |
| Age [years] | | | | | | | | | | | 0.9066 |
| <65 | 331 | 17 | 5.1 | 313 | 12 | 3.8 | 0.4258 | 0.75 ( 0.36, 1.54) | 0.74 ( 0.35, 1.57) | -0.01 (-0.04, 0.02) | |
| >=65 | 1670 | 89 | 5.3 | 1739 | 66 | 3.8 | 0.0316 | 0.71 ( 0.52, 0.97) | 0.70 ( 0.51, 0.97) | -0.02 (-0.03, 0.00) | |
| Region | | | | | | | | | | | 0.1269 |
| North America | 273 | 28 | 10.3 | 273 | 19 | 7.0 | 0.1697 | 0.68 ( 0.39, 1.19) | 0.65 ( 0.36, 1.20) | -0.03 (-0.08, 0.01) | |
| Latin America | 511 | 12 | 2.3 | 504 | 10 | 2.0 | 0.6903 | 0.84 ( 0.37, 1.94) | 0.84 ( 0.36, 1.97) | 0.00 (-0.02, 0.01) | |
| Europe | 865 | 41 | 4.7 | 894 | 20 | 2.2 | 0.0041 | 0.47 ( 0.28, 0.80) | 0.46 ( 0.27, 0.79) | -0.03 (-0.04,-0.01) | |
| Asia | 231 | 19 | 8.2 | 248 | 16 | 6.5 | 0.4561 | 0.78 ( 0.41, 1.49) | 0.77 ( 0.39, 1.54) | -0.02 (-0.06, 0.03) | |
| Other | 121 | 6 | 5.0 | 133 | 13 | 9.8 | 0.1451 | 1.97 ( 0.77, 5.02) | 2.08 ( 0.76, 5.65) | 0.05 (-0.02, 0.11) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.5986 |
| Diabetic | 1045 | 58 | 5.6 | 1081 | 46 | 4.3 | 0.1664 | 0.77 ( 0.53, 1.12) | 0.76 ( 0.51, 1.12) | -0.01 (-0.03, 0.01) | |
| Non-Diabetic | 956 | 48 | 5.0 | 971 | 32 | 3.3 | 0.0576 | 0.66 ( 0.42, 1.02) | 0.64 ( 0.41, 1.02) | -0.02 (-0.04, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.5398 |
| <30 | 1086 | 52 | 4.8 | 1094 | 41 | 3.7 | 0.2294 | 0.78 ( 0.52, 1.17) | 0.77 ( 0.51, 1.18) | -0.01 (-0.03, 0.01) | |
| >=30 | 915 | 54 | 5.9 | 958 | 37 | 3.9 | 0.0402 | 0.65 ( 0.44, 0.98) | 0.64 ( 0.42, 0.98) | -0.02 (-0.04, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.6566 |
| <130 | 827 | 48 | 5.8 | 853 | 33 | 3.9 | 0.0641 | 0.67 ( 0.43, 1.03) | 0.65 ( 0.41, 1.03) | -0.02 (-0.04, 0.00) | |
| >=130 | 1174 | 58 | 4.9 | 1199 | 45 | 3.8 | 0.1559 | 0.76 ( 0.52, 1.11) | 0.75 ( 0.50, 1.12) | -0.01 (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.2889 |
| <75 | 935 | 60 | 6.4 | 934 | 36 | 3.9 | 0.0121 | 0.60 ( 0.40, 0.90) | 0.58 ( 0.38, 0.89) | -0.03 (-0.05,-0.01) | |
| 75 to <85 | 657 | 29 | 4.4 | 703 | 23 | 3.3 | 0.2723 | 0.74 ( 0.43, 1.27) | 0.73 ( 0.42, 1.28) | -0.01 (-0.03, 0.01) | |
| >=85 | 409 | 17 | 4.2 | 415 | 19 | 4.6 | 0.7671 | 1.10 ( 0.58, 2.09) | 1.11 ( 0.57, 2.16) | 0.00 (-0.02, 0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Upper respiratory tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.3293 |
| <30 | 161 | 9 | 5.6 | 148 | 9 | 6.1 | 0.8539 | 1.09 ( 0.44, | 2.67) | 1.09 ( 0.42, | 2.83) | 0.00 (-0.05, 0.06) | |
| 30 to <45 | 550 | 29 | 5.3 | 564 | 15 | 2.7 | 0.0252 | 0.50 ( 0.27, | 0.93) | 0.49 ( 0.26, | 0.93) | -0.03 (-0.05, 0.00) | |
| >=45 | 1289 | 68 | 5.3 | 1340 | 54 | 4.0 | 0.1291 | 0.76 ( 0.54, | 1.08) | 0.75 ( 0.52, | 1.09) | -0.01 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.0399 |
| Normal (<30) | 764 | 47 | 6.2 | 787 | 21 | 2.7 | 0.0008 | 0.43 ( 0.26, | 0.72) | 0.42 ( 0.25, | 0.71) | -0.03 (-0.06,-0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 42 | 4.6 | 938 | 38 | 4.1 | 0.5887 | 0.89 ( 0.58, | 1.36) | 0.88 ( 0.56, | 1.38) | -0.01 (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 311 | 17 | 5.5 | 318 | 19 | 6.0 | 0.7837 | 1.09 ( 0.58, | 2.06) | 1.10 ( 0.56, | 2.16) | 0.01 (-0.03, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.3633 |
| Low, moderate or high | 1477 | 79 | 5.3 | 1548 | 55 | 3.6 | 0.0164 | 0.66 ( 0.47, | 0.93) | 0.65 ( 0.46, | 0.93) | -0.02 (-0.03, 0.00) | |
| Very high | 519 | 27 | 5.2 | 495 | 23 | 4.6 | 0.6828 | 0.89 ( 0.52, | 1.54) | 0.89 ( 0.50, | 1.57) | -0.01 (-0.03, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.2210 |
| No | 411 | 25 | 6.1 | 410 | 24 | 5.9 | 0.8898 | 0.96 ( 0.56, | 1.66) | 0.96 ( 0.54, | 1.71) | 0.00 (-0.03, 0.03) | |
| Yes | 1590 | 81 | 5.1 | 1642 | 54 | 3.3 | 0.0103 | 0.65 ( 0.46, | 0.90) | 0.63 ( 0.45, | 0.90) | -0.02 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.5261 |
| No | 282 | 11 | 3.9 | 277 | 10 | 3.6 | 0.8566 | 0.93 ( 0.40, | 2.14) | 0.92 ( 0.39, | 2.21) | 0.00 (-0.03, 0.03) | |
| Yes | 1719 | 95 | 5.5 | 1775 | 68 | 3.8 | 0.0175 | 0.69 ( 0.51, | 0.94) | 0.68 ( 0.50, | 0.94) | -0.02 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.1223 |
| No | 229 | 7 | 3.1 | 250 | 11 | 4.4 | 0.4400 | 1.44 ( 0.57, | 3.65) | 1.46 ( 0.56, | 3.83) | 0.01 (-0.02, 0.05) | |
| Yes | 1772 | 99 | 5.6 | 1802 | 67 | 3.7 | 0.0079 | 0.67 ( 0.49, | 0.90) | 0.65 ( 0.48, | 0.90) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: COVID-19

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 101 | 5.0 | 2052 | 96 | 4.7 | 0.5848 | 0.93 ( 0.71, 1.22) | 0.92 ( 0.69, 1.23) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Bronchitis

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 98 | 4.9 | 2052 | 70 | 3.4 | 0.0176 | 0.70 ( 0.52, 0.94) | 0.69 ( 0.50, 0.94) | -0.01 (-0.03, 0.00) | |
| Sex | | | | | | | | | | | 0.6841 |
| Male | 1065 | 45 | 4.2 | 1093 | 30 | 2.7 | 0.0605 | 0.65 ( 0.41, 1.02) | 0.64 ( 0.40, 1.02) | -0.01 (-0.03, 0.00) | |
| Female | 936 | 53 | 5.7 | 959 | 40 | 4.2 | 0.1330 | 0.74 ( 0.49, 1.10) | 0.73 ( 0.48, 1.10) | -0.01 (-0.03, 0.00) | |
| Age [years] | | | | | | | | | | | 0.8947 |
| <65 | 331 | 13 | 3.9 | 313 | 9 | 2.9 | 0.4626 | 0.73 ( 0.32, 1.69) | 0.72 ( 0.31, 1.72) | -0.01 (-0.04, 0.02) | |
| >=65 | 1670 | 85 | 5.1 | 1739 | 61 | 3.5 | 0.0226 | 0.69 ( 0.50, 0.95) | 0.68 ( 0.48, 0.95) | -0.02 (-0.03, 0.00) | |
| Region | | | | | | | | | | | 0.2791 |
| North America | 273 | 27 | 9.9 | 273 | 12 | 4.4 | 0.0127 | 0.44 ( 0.23, 0.86) | 0.42 ( 0.21, 0.85) | -0.05 (-0.10,-0.01) | |
| Latin America | 511 | 25 | 4.9 | 504 | 14 | 2.8 | 0.0797 | 0.57 ( 0.30, 1.08) | 0.56 ( 0.29, 1.08) | -0.02 (-0.04, 0.00) | |
| Europe | 865 | 39 | 4.5 | 894 | 33 | 3.7 | 0.3870 | 0.82 ( 0.52, 1.29) | 0.81 ( 0.51, 1.30) | -0.01 (-0.03, 0.01) | |
| Asia | 231 | 4 | 1.7 | 248 | 7 | 2.8 | 0.4257 | 1.63 ( 0.48, 5.50) | 1.65 ( 0.48, 5.71) | 0.01 (-0.02, 0.04) | |
| Other | 121 | 3 | 2.5 | 133 | 4 | 3.0 | 0.7973 | 1.21 ( 0.28, 5.31) | 1.22 ( 0.27, 5.56) | 0.01 (-0.03, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.2503 |
| Diabetic | 1045 | 53 | 5.1 | 1081 | 32 | 3.0 | 0.0130 | 0.58 ( 0.38, 0.90) | 0.57 ( 0.37, 0.89) | -0.02 (-0.04, 0.00) | |
| Non-Diabetic | 956 | 45 | 4.7 | 971 | 38 | 3.9 | 0.3909 | 0.83 ( 0.54, 1.27) | 0.82 ( 0.53, 1.28) | -0.01 (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.2442 |
| <30 | 1086 | 46 | 4.2 | 1094 | 26 | 2.4 | 0.0152 | 0.56 ( 0.35, 0.90) | 0.55 ( 0.34, 0.90) | -0.02 (-0.03, 0.00) | |
| >=30 | 915 | 52 | 5.7 | 958 | 44 | 4.6 | 0.2849 | 0.81 ( 0.55, 1.19) | 0.80 ( 0.53, 1.21) | -0.01 (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.9180 |
| <130 | 827 | 41 | 5.0 | 853 | 30 | 3.5 | 0.1423 | 0.71 ( 0.45, 1.12) | 0.70 ( 0.43, 1.13) | -0.01 (-0.03, 0.00) | |
| >=130 | 1174 | 57 | 4.9 | 1199 | 40 | 3.3 | 0.0617 | 0.69 ( 0.46, 1.02) | 0.68 ( 0.45, 1.02) | -0.02 (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.5014 |
| <75 | 935 | 56 | 6.0 | 934 | 37 | 4.0 | 0.0438 | 0.66 ( 0.44, 0.99) | 0.65 ( 0.42, 0.99) | -0.02 (-0.04, 0.00) | |
| 75 to <85 | 657 | 25 | 3.8 | 703 | 24 | 3.4 | 0.6989 | 0.90 ( 0.52, 1.55) | 0.89 ( 0.51, 1.58) | 0.00 (-0.02, 0.02) | |
| >=85 | 409 | 17 | 4.2 | 415 | 9 | 2.2 | 0.1027 | 0.52 ( 0.24, 1.16) | 0.51 ( 0.23, 1.16) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Bronchitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.1613 |
| <30 | 161 | 7 | 4.3 | 148 | 6 | 4.1 | 0.8978 | 0.93 ( 0.32, | 2.71) | 0.93 ( 0.31, | 2.83) | 0.00 (-0.05, 0.04) | |
| 30 to <45 | 550 | 26 | 4.7 | 564 | 27 | 4.8 | 0.9625 | 1.01 ( 0.60, | 1.71) | 1.01 ( 0.58, | 1.76) | 0.00 (-0.02, 0.03) | |
| >=45 | 1289 | 65 | 5.0 | 1340 | 37 | 2.8 | 0.0025 | 0.55 ( 0.37, | 0.81) | 0.53 ( 0.35, | 0.81) | -0.02 (-0.04,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.7398 |
| Normal (<30) | 764 | 39 | 5.1 | 787 | 32 | 4.1 | 0.3278 | 0.80 ( 0.50, | 1.26) | 0.79 ( 0.49, | 1.27) | -0.01 (-0.03, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 41 | 4.5 | 938 | 26 | 2.8 | 0.0520 | 0.62 ( 0.38, | 1.01) | 0.61 ( 0.37, | 1.01) | -0.02 (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 311 | 17 | 5.5 | 318 | 11 | 3.5 | 0.2223 | 0.63 ( 0.30, | 1.33) | 0.62 ( 0.29, | 1.35) | -0.02 (-0.05, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.5513 |
| Low, moderate or high | 1477 | 76 | 5.1 | 1548 | 52 | 3.4 | 0.0147 | 0.65 ( 0.46, | 0.92) | 0.64 ( 0.45, | 0.92) | -0.02 (-0.03, 0.00) | |
| Very high | 519 | 22 | 4.2 | 495 | 17 | 3.4 | 0.5054 | 0.81 ( 0.44, | 1.51) | 0.80 ( 0.42, | 1.53) | -0.01 (-0.03, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.1901 |
| No | 411 | 24 | 5.8 | 410 | 11 | 2.7 | 0.0252 | 0.46 ( 0.23, | 0.93) | 0.44 ( 0.21, | 0.92) | -0.03 (-0.06, 0.00) | |
| Yes | 1590 | 74 | 4.7 | 1642 | 59 | 3.6 | 0.1290 | 0.77 ( 0.55, | 1.08) | 0.76 ( 0.54, | 1.08) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.3899 |
| No | 282 | 18 | 6.4 | 277 | 9 | 3.2 | 0.0840 | 0.51 ( 0.23, | 1.11) | 0.49 ( 0.22, | 1.12) | -0.03 (-0.07, 0.00) | |
| Yes | 1719 | 80 | 4.7 | 1775 | 61 | 3.4 | 0.0676 | 0.74 ( 0.53, | 1.02) | 0.73 ( 0.52, | 1.02) | -0.01 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.2750 |
| No | 229 | 5 | 2.2 | 250 | 7 | 2.8 | 0.6662 | 1.28 ( 0.41, | 3.98) | 1.29 ( 0.40, | 4.12) | 0.01 (-0.02, 0.03) | |
| Yes | 1772 | 93 | 5.2 | 1802 | 63 | 3.5 | 0.0104 | 0.67 ( 0.49, | 0.91) | 0.65 ( 0.47, | 0.91) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Influenza

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 54 | 2.7 | 2052 | 42 | 2.0 | 0.1724 | 0.76 ( 0.51, 1.13) | 0.75 ( 0.50, 1.13) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Cellulitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 44 | 2.2 | 2052 | 48 | 2.3 | 0.7643 | 1.06 ( 0.71, 1.59) | 1.07 ( 0.70, 1.61) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Cystitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 43 | 2.1 | 2052 | 30 | 1.5 | 0.1002 | 0.68 ( 0.43, 1.08) | 0.68 ( 0.42, 1.08) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Gastroenteritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 28 | 1.4 | 2052 | 38 | 1.9 | 0.2551 | 1.32 ( 0.82, 2.15) | 1.33 ( 0.81, 2.17) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Sepsis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 24 | 1.2 | 2052 | 33 | 1.6 | 0.2692 | 1.34 ( 0.80, 2.26) | 1.35 ( 0.79, 2.29) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Herpes zoster

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 24 | 1.2 | 2052 | 30 | 1.5 | 0.4660 | 1.22 ( 0.72, 2.08) | 1.22 ( 0.71, 2.10) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Sinusitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 19 | 0.9 | 2052 | 23 | 1.1 | 0.5902 | 1.18 ( 0.64, 2.16) | 1.18 ( 0.64, 2.18) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: COVID-19 pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 19 | 0.9 | 2052 | 22 | 1.1 | 0.6966 | 1.13 ( 0.61, 2.08) | 1.13 ( 0.61, 2.10) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 516 | 25.8 | 2052 | 418 | 20.4 | <0.0001 | 0.79 ( 0.71, 0.88) | 0.74 ( 0.64, 0.85) | -0.05 (-0.08,-0.03) | |
| Sex | | | | | | | | | | | 0.3675 |
| Male | 1065 | 286 | 26.9 | 1093 | 221 | 20.2 | 0.0003 | 0.75 ( 0.65, 0.88) | 0.69 ( 0.56, 0.84) | -0.07 (-0.10,-0.03) | |
| Female | 936 | 230 | 24.6 | 959 | 197 | 20.5 | 0.0358 | 0.84 ( 0.71, 0.99) | 0.79 ( 0.64, 0.98) | -0.04 (-0.08, 0.00) | |
| Age [years] | | | | | | | | | | | 0.0320 |
| <65 | 331 | 71 | 21.5 | 313 | 71 | 22.7 | 0.7059 | 1.06 ( 0.79, 1.41) | 1.07 ( 0.74, 1.56) | 0.01 (-0.05, 0.08) | |
| >=65 | 1670 | 445 | 26.6 | 1739 | 347 | 20.0 | <0.0001 | 0.75 ( 0.66, 0.85) | 0.69 ( 0.58, 0.81) | -0.07 (-0.10,-0.04) | |
| Region | | | | | | | | | | | 0.7915 |
| North America | 273 | 55 | 20.1 | 273 | 48 | 17.6 | 0.4438 | 0.87 ( 0.62, 1.24) | 0.85 ( 0.55, 1.30) | -0.03 (-0.09, 0.04) | |
| Latin America | 511 | 135 | 26.4 | 504 | 114 | 22.6 | 0.1595 | 0.86 ( 0.69, 1.06) | 0.81 ( 0.61, 1.08) | -0.04 (-0.09, 0.01) | |
| Europe | 865 | 237 | 27.4 | 894 | 179 | 20.0 | 0.0003 | 0.73 ( 0.62, 0.87) | 0.66 ( 0.53, 0.83) | -0.07 (-0.11,-0.03) | |
| Asia | 231 | 56 | 24.2 | 248 | 47 | 19.0 | 0.1590 | 0.78 ( 0.55, 1.10) | 0.73 ( 0.47, 1.13) | -0.05 (-0.13, 0.02) | |
| Other | 121 | 33 | 27.3 | 133 | 30 | 22.6 | 0.3847 | 0.83 ( 0.54, 1.27) | 0.78 ( 0.44, 1.37) | -0.05 (-0.15, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.7394 |
| Diabetic | 1045 | 289 | 27.7 | 1081 | 232 | 21.5 | 0.0009 | 0.78 ( 0.67, 0.90) | 0.71 ( 0.59, 0.87) | -0.06 (-0.10,-0.03) | |
| Non-Diabetic | 956 | 227 | 23.7 | 971 | 186 | 19.2 | 0.0141 | 0.81 ( 0.68, 0.96) | 0.76 ( 0.61, 0.95) | -0.05 (-0.08,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.4809 |
| <30 | 1086 | 287 | 26.4 | 1094 | 220 | 20.1 | 0.0005 | 0.76 ( 0.65, 0.89) | 0.70 ( 0.57, 0.86) | -0.06 (-0.10,-0.03) | |
| >=30 | 915 | 229 | 25.0 | 958 | 198 | 20.7 | 0.0246 | 0.83 ( 0.70, 0.98) | 0.78 ( 0.63, 0.97) | -0.04 (-0.08,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.8490 |
| <130 | 827 | 228 | 27.6 | 853 | 188 | 22.0 | 0.0087 | 0.80 ( 0.68, 0.95) | 0.74 ( 0.59, 0.93) | -0.06 (-0.10,-0.01) | |
| >=130 | 1174 | 288 | 24.5 | 1199 | 230 | 19.2 | 0.0016 | 0.78 ( 0.67, 0.91) | 0.73 ( 0.60, 0.89) | -0.05 (-0.09,-0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.1208 |
| <75 | 935 | 244 | 26.1 | 934 | 217 | 23.2 | 0.1511 | 0.89 ( 0.76, 1.04) | 0.86 ( 0.69, 1.06) | -0.03 (-0.07, 0.01) | |
| 75 to <85 | 657 | 171 | 26.0 | 703 | 126 | 17.9 | 0.0003 | 0.69 ( 0.56, 0.84) | 0.62 ( 0.48, 0.80) | -0.08 (-0.12,-0.04) | |
| >=85 | 409 | 101 | 24.7 | 415 | 75 | 18.1 | 0.0204 | 0.73 ( 0.56, 0.95) | 0.67 ( 0.48, 0.94) | -0.07 (-0.12,-0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3800 |
| <30 | 161 | 51 | 31.7 | 148 | 44 | 29.7 | 0.7109 | 0.94 ( 0.67, 1.31) | 0.91 ( 0.56, 1.48) | -0.02 (-0.12, 0.08) | |
| 30 to <45 | 550 | 153 | 27.8 | 564 | 132 | 23.4 | 0.0914 | 0.84 ( 0.69, 1.03) | 0.79 ( 0.61, 1.04) | -0.04 (-0.10, 0.01) | |
| >=45 | 1289 | 312 | 24.2 | 1340 | 242 | 18.1 | 0.0001 | 0.75 ( 0.64, 0.87) | 0.69 ( 0.57, 0.83) | -0.06 (-0.09,-0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.4847 |
| Normal (<30) | 764 | 179 | 23.4 | 787 | 134 | 17.0 | 0.0017 | 0.73 ( 0.59, 0.89) | 0.67 ( 0.52, 0.86) | -0.06 (-0.10,-0.02) | |
| Microalbuminuria (30 to <=300) | 921 | 245 | 26.6 | 938 | 202 | 21.5 | 0.0106 | 0.81 ( 0.69, 0.95) | 0.76 ( 0.61, 0.94) | -0.05 (-0.09,-0.01) | |
| Macroalbuminuria (>300) | 311 | 91 | 29.3 | 318 | 82 | 25.8 | 0.3293 | 0.88 ( 0.68, 1.14) | 0.84 ( 0.59, 1.19) | -0.03 (-0.10, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.1195 |
| Low, moderate or high | 1477 | 358 | 24.2 | 1548 | 282 | 18.2 | <0.0001 | 0.75 ( 0.65, 0.86) | 0.70 ( 0.58, 0.83) | -0.06 (-0.09,-0.03) | |
| Very high | 519 | 157 | 30.3 | 495 | 136 | 27.5 | 0.3297 | 0.91 ( 0.75, 1.10) | 0.87 ( 0.67, 1.15) | -0.03 (-0.08, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.1296 |
| No | 411 | 114 | 27.7 | 410 | 105 | 25.6 | 0.4907 | 0.92 ( 0.74, 1.16) | 0.90 ( 0.66, 1.22) | -0.02 (-0.08, 0.04) | |
| Yes | 1590 | 402 | 25.3 | 1642 | 313 | 19.1 | <0.0001 | 0.75 ( 0.66, 0.86) | 0.70 ( 0.59, 0.82) | -0.06 (-0.09,-0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.1478 |
| No | 282 | 72 | 25.5 | 277 | 68 | 24.5 | 0.7885 | 0.96 ( 0.72, 1.28) | 0.95 ( 0.65, 1.39) | -0.01 (-0.08, 0.06) | |
| Yes | 1719 | 444 | 25.8 | 1775 | 350 | 19.7 | <0.0001 | 0.76 ( 0.67, 0.86) | 0.71 ( 0.60, 0.83) | -0.06 (-0.09,-0.03) | |
| Baseline use of diuretics | | | | | | | | | | | 0.8025 |
| No | 229 | 39 | 17.0 | 250 | 32 | 12.8 | 0.1930 | 0.75 ( 0.49, 1.16) | 0.72 ( 0.43, 1.19) | -0.04 (-0.11, 0.02) | |
| Yes | 1772 | 477 | 26.9 | 1802 | 386 | 21.4 | 0.0001 | 0.80 ( 0.71, 0.89) | 0.74 ( 0.63, 0.86) | -0.05 (-0.08,-0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 172 | 8.6 | 2052 | 172 | 8.4 | 0.8072 | 0.98 ( 0.80, 1.19) | 0.97 ( 0.78, 1.21) | 0.00 (-0.02, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 72 | 3.6 | 2052 | 57 | 2.8 | 0.1369 | 0.77 ( 0.55, 1.09) | 0.77 ( 0.54, 1.09) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina pectoris

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 48 | 2.4 | 2052 | 55 | 2.7 | 0.5691 | 1.12 ( 0.76, 1.64) | 1.12 ( 0.76, 1.66) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 47 | 2.3 | 2052 | 50 | 2.4 | 0.8549 | 1.04 ( 0.70, 1.54) | 1.04 ( 0.69, 1.55) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure chronic

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 33 | 1.6 | 2052 | 39 | 1.9 | 0.5447 | 1.15 ( 0.73, 1.82) | 1.16 ( 0.72, 1.84) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 21 | 1.0 | 2052 | 33 | 1.6 | 0.1209 | 1.53 ( 0.89, 2.64) | 1.54 ( 0.89, 2.67) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 32 | 1.6 | 2052 | 19 | 0.9 | 0.0545 | 0.58 ( 0.33, 1.02) | 0.58 ( 0.32, 1.02) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Bradycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 26 | 1.3 | 2052 | 30 | 1.5 | 0.6574 | 1.13 ( 0.67, 1.90) | 1.13 ( 0.66, 1.91) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Coronary artery disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 28 | 1.4 | 2052 | 20 | 1.0 | 0.2115 | 0.70 ( 0.39, 1.23) | 0.69 ( 0.39, 1.24) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial flutter

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 25 | 1.2 | 2052 | 27 | 1.3 | 0.8510 | 1.05 ( 0.61, 1.81) | 1.05 ( 0.61, 1.82) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina unstable

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 16 | 0.8 | 2052 | 23 | 1.1 | 0.2949 | 1.40 ( 0.74, 2.65) | 1.41 ( 0.74, 2.67) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Palpitations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 21 | 1.0 | 2052 | 19 | 0.9 | 0.6908 | 0.88 ( 0.48, 1.64) | 0.88 ( 0.47, 1.64) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 21 | 1.0 | 2052 | 19 | 0.9 | 0.6908 | 0.88 ( 0.48, 1.64) | 0.88 ( 0.47, 1.64) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperkalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 186 | 9.3 | 2052 | 163 | 7.9 | 0.1251 | 0.85 ( 0.70, 1.04) | 0.84 ( 0.68, 1.05) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 160 | 8.0 | 2052 | 133 | 6.5 | 0.0627 | 0.81 ( 0.65, 1.01) | 0.80 ( 0.63, 1.01) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperuricaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 148 | 7.4 | 2052 | 117 | 5.7 | 0.0291 | 0.77 | ( 0.61, 0.97) | 0.76 | ( 0.59, 0.97) | -0.02 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.6007 |
| Male | 1065 | 75 | 7.0 | 1093 | 63 | 5.8 | 0.2250 | 0.82 | ( 0.59, 1.13) | 0.81 | ( 0.57, 1.14) | -0.01 | (-0.03, 0.01) | |
| Female | 936 | 73 | 7.8 | 959 | 54 | 5.6 | 0.0591 | 0.72 | ( 0.51, 1.01) | 0.71 | ( 0.49, 1.02) | -0.02 | (-0.04, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.0010 |
| <65 | 331 | 29 | 8.8 | 313 | 41 | 13.1 | 0.0771 | 1.50 | ( 0.95, 2.34) | 1.57 | ( 0.95, 2.60) | 0.04 | ( 0.00, 0.09) | |
| >=65 | 1670 | 119 | 7.1 | 1739 | 76 | 4.4 | 0.0005 | 0.61 | ( 0.46, 0.81) | 0.60 | ( 0.44, 0.80) | -0.03 | (-0.04,-0.01) | |
| Region | | | | | | | | | | | | | | 0.3704 |
| North America | 273 | 8 | 2.9 | 273 | 6 | 2.2 | 0.5882 | 0.75 | ( 0.26, 2.13) | 0.74 | ( 0.25, 2.17) | -0.01 | (-0.03, 0.02) | |
| Latin America | 511 | 66 | 12.9 | 504 | 60 | 11.9 | 0.6252 | 0.92 | ( 0.66, 1.28) | 0.91 | ( 0.63, 1.32) | -0.01 | (-0.05, 0.03) | |
| Europe | 865 | 51 | 5.9 | 894 | 32 | 3.6 | 0.0220 | 0.61 | ( 0.39, 0.94) | 0.59 | ( 0.38, 0.93) | -0.02 | (-0.04, 0.00) | |
| Asia | 231 | 18 | 7.8 | 248 | 11 | 4.4 | 0.1237 | 0.57 | ( 0.27, 1.18) | 0.55 | ( 0.25, 1.19) | -0.03 | (-0.08, 0.01) | |
| Other | 121 | 5 | 4.1 | 133 | 8 | 6.0 | 0.4965 | 1.46 | ( 0.49, 4.33) | 1.48 | ( 0.47, 4.67) | 0.02 | (-0.03, 0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0065 |
| Diabetic | 1045 | 74 | 7.1 | 1081 | 78 | 7.2 | 0.9044 | 1.02 | ( 0.75, 1.38) | 1.02 | ( 0.73, 1.42) | 0.00 | (-0.02, 0.02) | |
| Non-Diabetic | 956 | 74 | 7.7 | 971 | 39 | 4.0 | 0.0005 | 0.52 | ( 0.36, 0.76) | 0.50 | ( 0.33, 0.74) | -0.04 | (-0.06,-0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3664 |
| <30 | 1086 | 79 | 7.3 | 1094 | 55 | 5.0 | 0.0290 | 0.69 | ( 0.49, 0.96) | 0.67 | ( 0.47, 0.96) | -0.02 | (-0.04, 0.00) | |
| >=30 | 915 | 69 | 7.5 | 958 | 62 | 6.5 | 0.3645 | 0.86 | ( 0.62, 1.19) | 0.85 | ( 0.59, 1.21) | -0.01 | (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0932 |
| <130 | 827 | 57 | 6.9 | 853 | 57 | 6.7 | 0.8641 | 0.97 | ( 0.68, 1.38) | 0.97 | ( 0.66, 1.41) | 0.00 | (-0.03, 0.02) | |
| >=130 | 1174 | 91 | 7.8 | 1199 | 60 | 5.0 | 0.0061 | 0.65 | ( 0.47, 0.89) | 0.63 | ( 0.45, 0.88) | -0.03 | (-0.05,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3478 |
| <75 | 935 | 79 | 8.4 | 934 | 58 | 6.2 | 0.0633 | 0.73 | ( 0.53, 1.02) | 0.72 | ( 0.50, 1.02) | -0.02 | (-0.05, 0.00) | |
| 75 to <85 | 657 | 48 | 7.3 | 703 | 35 | 5.0 | 0.0732 | 0.68 | ( 0.45, 1.04) | 0.66 | ( 0.42, 1.04) | -0.02 | (-0.05, 0.00) | |
| >=85 | 409 | 21 | 5.1 | 415 | 24 | 5.8 | 0.6820 | 1.13 | ( 0.64, 1.99) | 1.13 | ( 0.62, 2.07) | 0.01 | (-0.02, 0.04) | |

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MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperuricaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.3830 |
| <30 | 161 | 20 | 12.4 | 148 | 20 | 13.5 | 0.7753 | 1.09 ( 0.61, | 1.94) | 1.10 ( 0.57, | 2.14) | 0.01 (-0.06, 0.09) | |
| 30 to <45 | 550 | 44 | 8.0 | 564 | 37 | 6.6 | 0.3548 | 0.82 ( 0.54, | 1.25) | 0.81 ( 0.51, | 1.27) | -0.01 (-0.04, 0.02) | |
| >=45 | 1289 | 84 | 6.5 | 1340 | 60 | 4.5 | 0.0216 | 0.69 ( 0.50, | 0.95) | 0.67 ( 0.48, | 0.95) | -0.02 (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.0905 |
| Normal (<30) | 764 | 59 | 7.7 | 787 | 34 | 4.3 | 0.0048 | 0.56 ( 0.37, | 0.84) | 0.54 ( 0.35, | 0.83) | -0.03 (-0.06,-0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 59 | 6.4 | 938 | 50 | 5.3 | 0.3237 | 0.83 ( 0.58, | 1.20) | 0.82 ( 0.56, | 1.21) | -0.01 (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 311 | 29 | 9.3 | 318 | 33 | 10.4 | 0.6579 | 1.11 ( 0.69, | 1.79) | 1.13 ( 0.67, | 1.90) | 0.01 (-0.04, 0.06) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.0104 |
| Low, moderate or high | 1477 | 102 | 6.9 | 1548 | 66 | 4.3 | 0.0015 | 0.62 ( 0.46, | 0.83) | 0.60 ( 0.44, | 0.83) | -0.03 (-0.04,-0.01) | |
| Very high | 519 | 46 | 8.9 | 495 | 51 | 10.3 | 0.4359 | 1.16 ( 0.80, | 1.70) | 1.18 ( 0.78, | 1.80) | 0.01 (-0.02, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.1105 |
| No | 411 | 32 | 7.8 | 410 | 16 | 3.9 | 0.0177 | 0.50 ( 0.28, | 0.90) | 0.48 ( 0.26, | 0.89) | -0.04 (-0.07,-0.01) | |
| Yes | 1590 | 116 | 7.3 | 1642 | 101 | 6.2 | 0.1937 | 0.84 ( 0.65, | 1.09) | 0.83 ( 0.63, | 1.10) | -0.01 (-0.03, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.4419 |
| No | 282 | 19 | 6.7 | 277 | 11 | 4.0 | 0.1467 | 0.59 ( 0.29, | 1.22) | 0.57 ( 0.27, | 1.23) | -0.03 (-0.06, 0.01) | |
| Yes | 1719 | 129 | 7.5 | 1775 | 106 | 6.0 | 0.0706 | 0.80 ( 0.62, | 1.02) | 0.78 ( 0.60, | 1.02) | -0.02 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.5810 |
| No | 229 | 8 | 3.5 | 250 | 5 | 2.0 | 0.3150 | 0.57 ( 0.19, | 1.72) | 0.56 ( 0.18, | 1.75) | -0.01 (-0.04, 0.01) | |
| Yes | 1772 | 140 | 7.9 | 1802 | 112 | 6.2 | 0.0491 | 0.79 ( 0.62, | <1.00) | 0.77 ( 0.60, | 1.00) | -0.02 (-0.03, 0.00) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypoglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 83 | 4.1 | 2052 | 83 | 4.0 | 0.8685 | 0.98 ( 0.72, 1.31) | 0.97 ( 0.71, 1.33) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Gout

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 80 | 4.0 | 2052 | 55 | 2.7 | 0.0194 | 0.67 ( 0.48, | 0.94) | 0.66 ( 0.47, | 0.94) | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | 0.0040 |
| Male | 1065 | 43 | 4.0 | 1093 | 43 | 3.9 | 0.9023 | 0.97 ( 0.64, | 1.47) | 0.97 ( 0.63, | 1.50) | 0.00 (-0.02, 0.02) | |
| Female | 936 | 37 | 4.0 | 959 | 12 | 1.3 | 0.0002 | 0.32 ( 0.17, | 0.60) | 0.31 ( 0.16, | 0.59) | -0.03 (-0.04,-0.01) | |
| Age [years] | | | | | | | | | | | | | 0.0513 |
| <65 | 331 | 11 | 3.3 | 313 | 14 | 4.5 | 0.4503 | 1.35 ( 0.62, | 2.92) | 1.36 ( 0.61, | 3.05) | 0.01 (-0.02, 0.04) | |
| >=65 | 1670 | 69 | 4.1 | 1739 | 41 | 2.4 | 0.0034 | 0.57 ( 0.39, | 0.83) | 0.56 ( 0.38, | 0.83) | -0.02 (-0.03,-0.01) | |
| Region | | | | | | | | | | | | | 0.3714 |
| North America | 273 | 23 | 8.4 | 273 | 14 | 5.1 | 0.1254 | 0.61 ( 0.32, | 1.16) | 0.59 ( 0.30, | 1.17) | -0.03 (-0.08, 0.01) | |
| Latin America | 511 | 11 | 2.2 | 504 | 6 | 1.2 | 0.2324 | 0.55 ( 0.21, | 1.48) | 0.55 ( 0.20, | 1.49) | -0.01 (-0.03, 0.01) | |
| Europe | 865 | 24 | 2.8 | 894 | 18 | 2.0 | 0.2959 | 0.73 ( 0.40, | 1.33) | 0.72 ( 0.39, | 1.34) | -0.01 (-0.02, 0.01) | |
| Asia | 231 | 5 | 2.2 | 248 | 9 | 3.6 | 0.3417 | 1.68 ( 0.57, | 4.93) | 1.70 ( 0.56, | 5.16) | 0.01 (-0.02, 0.04) | |
| Other | 121 | 17 | 14.0 | 133 | 8 | 6.0 | 0.0318 | 0.43 ( 0.19, | 0.96) | 0.39 ( 0.16, | 0.94) | -0.08 (-0.15,-0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.6256 |
| Diabetic | 1045 | 37 | 3.5 | 1081 | 28 | 2.6 | 0.2032 | 0.73 ( 0.45, | 1.19) | 0.72 ( 0.44, | 1.19) | -0.01 (-0.02, 0.01) | |
| Non-Diabetic | 956 | 43 | 4.5 | 971 | 27 | 2.8 | 0.0440 | 0.62 ( 0.39, | 0.99) | 0.61 ( 0.37, | 0.99) | -0.02 (-0.03, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.5656 |
| <30 | 1086 | 44 | 4.1 | 1094 | 27 | 2.5 | 0.0373 | 0.61 ( 0.38, | 0.98) | 0.60 ( 0.37, | 0.97) | -0.02 (-0.03, 0.00) | |
| >=30 | 915 | 36 | 3.9 | 958 | 28 | 2.9 | 0.2283 | 0.74 ( 0.46, | 1.21) | 0.74 ( 0.44, | 1.21) | -0.01 (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.8932 |
| <130 | 827 | 40 | 4.8 | 853 | 27 | 3.2 | 0.0801 | 0.65 ( 0.41, | 1.06) | 0.64 ( 0.39, | 1.06) | -0.02 (-0.04, 0.00) | |
| >=130 | 1174 | 40 | 3.4 | 1199 | 28 | 2.3 | 0.1176 | 0.69 ( 0.43, | 1.10) | 0.68 ( 0.42, | 1.11) | -0.01 (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.7560 |
| <75 | 935 | 41 | 4.4 | 934 | 31 | 3.3 | 0.2312 | 0.76 ( 0.48, | 1.20) | 0.75 ( 0.47, | 1.20) | -0.01 (-0.03, 0.01) | |
| 75 to <85 | 657 | 27 | 4.1 | 703 | 17 | 2.4 | 0.0781 | 0.59 ( 0.32, | 1.07) | 0.58 ( 0.31, | 1.07) | -0.02 (-0.04, 0.00) | |
| >=85 | 409 | 12 | 2.9 | 415 | 7 | 1.7 | 0.2330 | 0.57 ( 0.23, | 1.45) | 0.57 ( 0.22, | 1.46) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Gout

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.6433 |
| <30 | 161 | 10 | 6.2 | 148 | 9 | 6.1 | 0.9621 | 0.98 ( 0.41, | 2.34) | 0.98 ( 0.39, | 2.48) | 0.00 (-0.05, 0.05) | |
| 30 to <45 | 550 | 31 | 5.6 | 564 | 19 | 3.4 | 0.0676 | 0.60 ( 0.34, | 1.05) | 0.58 ( 0.33, | 1.05) | -0.02 (-0.05, 0.00) | |
| >=45 | 1289 | 39 | 3.0 | 1340 | 27 | 2.0 | 0.0977 | 0.67 ( 0.41, | 1.08) | 0.66 ( 0.40, | 1.08) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.0506 |
| Normal (<30) | 764 | 39 | 5.1 | 787 | 18 | 2.3 | 0.0032 | 0.45 ( 0.26, | 0.78) | 0.44 ( 0.25, | 0.77) | -0.03 (-0.05,-0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 34 | 3.7 | 938 | 25 | 2.7 | 0.2069 | 0.72 ( 0.43, | 1.20) | 0.71 ( 0.42, | 1.21) | -0.01 (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 311 | 7 | 2.3 | 318 | 12 | 3.8 | 0.2646 | 1.68 ( 0.67, | 4.20) | 1.70 ( 0.66, | 4.38) | 0.02 (-0.01, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.1462 |
| Low, moderate or high | 1477 | 53 | 3.6 | 1548 | 31 | 2.0 | 0.0080 | 0.56 ( 0.36, | 0.86) | 0.55 ( 0.35, | 0.86) | -0.02 (-0.03, 0.00) | |
| Very high | 519 | 27 | 5.2 | 495 | 24 | 4.8 | 0.7966 | 0.93 ( 0.55, | 1.59) | 0.93 ( 0.53, | 1.63) | 0.00 (-0.03, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.8561 |
| No | 411 | 25 | 6.1 | 410 | 16 | 3.9 | 0.1516 | 0.64 ( 0.35, | 1.18) | 0.63 ( 0.33, | 1.19) | -0.02 (-0.05, 0.01) | |
| Yes | 1590 | 55 | 3.5 | 1642 | 39 | 2.4 | 0.0667 | 0.69 ( 0.46, | 1.03) | 0.68 ( 0.45, | 1.03) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.9778 |
| No | 282 | 9 | 3.2 | 277 | 6 | 2.2 | 0.4532 | 0.68 ( 0.24, | 1.88) | 0.67 ( 0.24, | 1.91) | -0.01 (-0.04, 0.02) | |
| Yes | 1719 | 71 | 4.1 | 1775 | 49 | 2.8 | 0.0262 | 0.67 ( 0.47, | 0.96) | 0.66 ( 0.46, | 0.95) | -0.01 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.6985 |
| No | 229 | 3 | 1.3 | 250 | 3 | 1.2 | 0.9139 | 0.92 ( 0.19, | 4.49) | 0.91 ( 0.18, | 4.58) | 0.00 (-0.02, 0.02) | |
| Yes | 1772 | 77 | 4.3 | 1802 | 52 | 2.9 | 0.0193 | 0.66 ( 0.47, | 0.94) | 0.65 ( 0.46, | 0.94) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypokalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 62 | 3.1 | 2052 | 74 | 3.6 | 0.3695 | 1.16 ( 0.84, 1.62) | 1.17 ( 0.83, 1.65) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Dehydration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 42 | 2.1 | 2052 | 57 | 2.8 | 0.1616 | 1.32 ( 0.89, 1.96) | 1.33 ( 0.89, 1.99) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyponatraemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 34 | 1.7 | 2052 | 25 | 1.2 | 0.2013 | 0.72 ( 0.43, 1.20) | 0.71 ( 0.42, 1.20) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Type 2 diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 2001 | 33 | 1.6 | 2052 | 18 | 0.9 | 0.0275 | 0.53 ( 0.30, 0.94) | 0.53 ( 0.30, 0.94) | -0.01 (-0.01, 0.00) | | |
| Sex | | | | | | | | | | | | 0.0192 |
| Male | 1065 | 14 | 1.3 | 1093 | 14 | 1.3 | 0.9449 | 0.97 ( 0.47, 2.03) | 0.97 ( 0.46, 2.05) | 0.00 (-0.01, 0.01) | | |
| Female | 936 | 19 | 2.0 | 959 | 4 | 0.4 | 0.0013 | 0.21 ( 0.07, 0.60) | 0.20 ( 0.07, 0.60) | -0.02 (-0.03,-0.01) | | |
| Age [years] | | | | | | | | | | | | 0.7698 |
| <65 | 331 | 5 | 1.5 | 313 | 2 | 0.6 | 0.2863 | 0.42 ( 0.08, 2.16) | 0.42 ( 0.08, 2.18) | -0.01 (-0.02, 0.01) | | |
| >=65 | 1670 | 28 | 1.7 | 1739 | 16 | 0.9 | 0.0504 | 0.55 ( 0.30, 1.01) | 0.54 ( 0.29, 1.01) | -0.01 (-0.02, 0.00) | | |
| Region | | | | | | | | | | | | 0.5762 |
| North America | 273 | 2 | 0.7 | 273 | 2 | 0.7 | 1.0000 | 1.00 ( 0.14, 7.05) | 1.00 ( 0.14, 7.15) | 0.00 (-0.01, 0.01) | | |
| Latin America | 511 | 11 | 2.2 | 504 | 4 | 0.8 | 0.0728 | 0.37 ( 0.12, 1.15) | 0.36 ( 0.12, 1.15) | -0.01 (-0.03, 0.00) | | |
| Europe | 865 | 17 | 2.0 | 894 | 8 | 0.9 | 0.0579 | 0.46 ( 0.20, 1.05) | 0.45 ( 0.19, 1.05) | -0.01 (-0.02, 0.00) | | |
| Asia | 231 | 3 | 1.3 | 248 | 2 | 0.8 | 0.5963 | 0.62 ( 0.10, 3.68) | 0.62 ( 0.10, 3.73) | 0.00 (-0.02, 0.01) | | |
| Other | 121 | 0 | 0 | 133 | 2 | 1.5 | 0.2797 | 4.55 ( 0.22, 93.88) | 4.62 ( 0.22, 97.19) | 0.01 (-0.01, 0.04) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.8818 |
| Diabetic | 1045 | 12 | 1.1 | 1081 | 7 | 0.6 | 0.2200 | 0.56 ( 0.22, 1.43) | 0.56 ( 0.22, 1.43) | -0.01 (-0.01, 0.00) | | |
| Non-Diabetic | 956 | 21 | 2.2 | 971 | 11 | 1.1 | 0.0677 | 0.52 ( 0.25, 1.06) | 0.51 ( 0.24, 1.06) | -0.01 (-0.02, 0.00) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9502 |
| <30 | 1086 | 22 | 2.0 | 1094 | 12 | 1.1 | 0.0801 | 0.54 ( 0.27, 1.09) | 0.54 ( 0.26, 1.09) | -0.01 (-0.02, 0.00) | | |
| >=30 | 915 | 11 | 1.2 | 958 | 6 | 0.6 | 0.1890 | 0.52 ( 0.19, 1.40) | 0.52 ( 0.19, 1.41) | -0.01 (-0.01, 0.00) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1711 |
| <130 | 827 | 10 | 1.2 | 853 | 9 | 1.1 | 0.7652 | 0.87 ( 0.36, 2.14) | 0.87 ( 0.35, 2.15) | 0.00 (-0.01, 0.01) | | |
| >=130 | 1174 | 23 | 2.0 | 1199 | 9 | 0.8 | 0.0107 | 0.38 ( 0.18, 0.82) | 0.38 ( 0.17, 0.82) | -0.01 (-0.02, 0.00) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2267 |
| <75 | 935 | 13 | 1.4 | 934 | 10 | 1.1 | 0.5308 | 0.77 ( 0.34, 1.75) | 0.77 ( 0.33, 1.76) | 0.00 (-0.01, 0.01) | | |
| 75 to <85 | 657 | 13 | 2.0 | 703 | 3 | 0.4 | 0.0080 | 0.22 ( 0.06, 0.75) | 0.21 ( 0.06, 0.75) | -0.02 (-0.03, 0.00) | | |
| >=85 | 409 | 7 | 1.7 | 415 | 5 | 1.2 | 0.5438 | 0.70 ( 0.23, 2.20) | 0.70 ( 0.22, 2.22) | -0.01 (-0.02, 0.01) | | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Metabolism and nutrition disorders
Preferred term: Type 2 diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.5423 |
| <30 | 161 | 2 | 1.2 | 148 | 1 | 0.7 | 0.6119 | 0.54 ( 0.05, | 5.94) | 0.54 ( 0.05, | 6.03) | -0.01 (-0.03, 0.02) | |
| 30 to <45 | 550 | 8 | 1.5 | 564 | 2 | 0.4 | 0.0517 | 0.24 ( 0.05, | 1.14) | 0.24 ( 0.05, | 1.14) | -0.01 (-0.02, 0.00) | |
| >=45 | 1289 | 23 | 1.8 | 1340 | 15 | 1.1 | 0.1533 | 0.63 ( 0.33, | 1.20) | 0.62 ( 0.32, | 1.20) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.8654 |
| Normal (<30) | 764 | 16 | 2.1 | 787 | 9 | 1.1 | 0.1372 | 0.55 ( 0.24, | 1.23) | 0.54 ( 0.24, | 1.23) | -0.01 (-0.02, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 13 | 1.4 | 938 | 6 | 0.6 | 0.0981 | 0.45 ( 0.17, | 1.19) | 0.45 ( 0.17, | 1.19) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 311 | 4 | 1.3 | 318 | 3 | 0.9 | 0.6820 | 0.73 ( 0.17, | 3.25) | 0.73 ( 0.16, | 3.29) | 0.00 (-0.02, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.9886 |
| Low, moderate or high | 1477 | 27 | 1.8 | 1548 | 15 | 1.0 | 0.0436 | 0.53 ( 0.28, | 0.99) | 0.53 ( 0.28, | 0.99) | -0.01 (-0.02, 0.00) | |
| Very high | 519 | 6 | 1.2 | 495 | 3 | 0.6 | 0.3506 | 0.52 ( 0.13, | 2.08) | 0.52 ( 0.13, | 2.10) | -0.01 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.3432 |
| No | 411 | 5 | 1.2 | 410 | 1 | 0.2 | 0.1018 | 0.20 ( 0.02, | 1.71) | 0.20 ( 0.02, | 1.71) | -0.01 (-0.02, 0.00) | |
| Yes | 1590 | 28 | 1.8 | 1642 | 17 | 1.0 | 0.0784 | 0.59 ( 0.32, | 1.07) | 0.58 ( 0.32, | 1.07) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.4950 |
| No | 282 | 2 | 0.7 | 277 | 2 | 0.7 | 0.9857 | 1.02 ( 0.14, | 7.18) | 1.02 ( 0.14, | 7.28) | 0.00 (-0.01, 0.01) | |
| Yes | 1719 | 31 | 1.8 | 1775 | 16 | 0.9 | 0.0207 | 0.50 ( 0.27, | 0.91) | 0.50 ( 0.27, | 0.91) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.5709 |
| No | 229 | 2 | 0.9 | 250 | 2 | 0.8 | 0.9298 | 0.92 ( 0.13, | 6.45) | 0.92 ( 0.13, | 6.55) | 0.00 (-0.02, 0.02) | |
| Yes | 1772 | 31 | 1.7 | 1802 | 16 | 0.9 | 0.0238 | 0.51 ( 0.28, | 0.92) | 0.50 ( 0.27, | 0.92) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 29 | 1.4 | 2052 | 32 | 1.6 | 0.7733 | 1.08 ( 0.65, 1.77) | 1.08 ( 0.65, 1.79) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypomagnesaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 28 | 1.4 | 2052 | 11 | 0.5 | 0.0049 | 0.38 ( 0.19, 0.77) | | 0.38 ( 0.19, 0.76) | | -0.01 (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | 0.7994 |
| Male | 1065 | 14 | 1.3 | 1093 | 6 | 0.5 | 0.0635 | 0.42 ( 0.16, 1.08) | | 0.41 ( 0.16, 1.08) | | -0.01 (-0.02, 0.00) | |
| Female | 936 | 14 | 1.5 | 959 | 5 | 0.5 | 0.0333 | 0.35 ( 0.13, 0.96) | | 0.35 ( 0.12, 0.96) | | -0.01 (-0.02, 0.00) | |
| Age [years] | | | | | | | | | | | | | 0.9434 |
| <65 | 331 | 3 | 0.9 | 313 | 1 | 0.3 | 0.3434 | 0.35 ( 0.04, 3.37) | | 0.35 ( 0.04, 3.39) | | -0.01 (-0.02, 0.01) | |
| >=65 | 1670 | 25 | 1.5 | 1739 | 10 | 0.6 | 0.0076 | 0.38 ( 0.19, 0.80) | | 0.38 ( 0.18, 0.79) | | -0.01 (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | 0.8965 |
| North America | 273 | 8 | 2.9 | 273 | 3 | 1.1 | 0.1278 | 0.38 ( 0.10, 1.40) | | 0.37 ( 0.10, 1.40) | | -0.02 (-0.04, 0.01) | |
| Latin America | 511 | 7 | 1.4 | 504 | 2 | 0.4 | 0.0983 | 0.29 ( 0.06, 1.39) | | 0.29 ( 0.06, 1.39) | | -0.01 (-0.02, 0.00) | |
| Europe | 865 | 11 | 1.3 | 894 | 4 | 0.4 | 0.0602 | 0.35 ( 0.11, 1.10) | | 0.35 ( 0.11, 1.10) | | -0.01 (-0.02, 0.00) | |
| Asia | 231 | 0 | 0 | 248 | 0 | 0 | 0.9718 | 0.93 ( 0.02, 46.76) | | 0.93 ( 0.02, 47.14) | | 0.00 (-0.01, 0.01) | |
| Other | 121 | 2 | 1.7 | 133 | 2 | 1.5 | 0.9240 | 0.91 ( 0.13, 6.36) | | 0.91 ( 0.13, 6.55) | | 0.00 (-0.03, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.2156 |
| Diabetic | 1045 | 23 | 2.2 | 1081 | 7 | 0.6 | 0.0024 | 0.29 ( 0.13, 0.68) | | 0.29 ( 0.12, 0.68) | | -0.02 (-0.03,-0.01) | |
| Non-Diabetic | 956 | 5 | 0.5 | 971 | 4 | 0.4 | 0.7207 | 0.79 ( 0.21, 2.92) | | 0.79 ( 0.21, 2.94) | | 0.00 (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.9129 |
| <30 | 1086 | 15 | 1.4 | 1094 | 6 | 0.5 | 0.0465 | 0.40 ( 0.15, 1.02) | | 0.39 ( 0.15, 1.02) | | -0.01 (-0.02, 0.00) | |
| >=30 | 915 | 13 | 1.4 | 958 | 5 | 0.5 | 0.0462 | 0.37 ( 0.13, 1.03) | | 0.36 ( 0.13, 1.03) | | -0.01 (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.3958 |
| <130 | 827 | 11 | 1.3 | 853 | 6 | 0.7 | 0.1994 | 0.53 ( 0.20, 1.42) | | 0.53 ( 0.19, 1.43) | | -0.01 (-0.02, 0.00) | |
| >=130 | 1174 | 17 | 1.4 | 1199 | 5 | 0.4 | 0.0088 | 0.29 ( 0.11, 0.78) | | 0.29 ( 0.10, 0.78) | | -0.01 (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.5396 |
| <75 | 935 | 19 | 2.0 | 934 | 6 | 0.6 | 0.0089 | 0.32 ( 0.13, 0.79) | | 0.31 ( 0.12, 0.78) | | -0.01 (-0.02, 0.00) | |
| 75 to <85 | 657 | 7 | 1.1 | 703 | 5 | 0.7 | 0.4852 | 0.67 ( 0.21, 2.09) | | 0.67 ( 0.21, 2.11) | | 0.00 (-0.01, 0.01) | |
| >=85 | 409 | 2 | 0.5 | 415 | 0 | 0 | 0.2422 | 0.20 (<0.01, 4.09) | | 0.20 (<0.01, 4.10) | | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypomagnesaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3205 |
| <30 | 161 | 0 | 0 | 148 | 1 | 0.7 | 0.4417 | 3.26 ( 0.13, 79.45) | 3.28 ( 0.13, 81.26) | 0.01 (-0.01, 0.03) | |
| 30 to <45 | 550 | 9 | 1.6 | 564 | 2 | 0.4 | 0.0305 | 0.22 ( 0.05, <1.00) | 0.21 ( 0.05, 0.99) | -0.01 (-0.02, 0.00) | |
| >=45 | 1289 | 19 | 1.5 | 1340 | 8 | 0.6 | 0.0258 | 0.41 ( 0.18, 0.92) | 0.40 ( 0.18, 0.92) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.7946 |
| Normal (<30) | 764 | 11 | 1.4 | 787 | 5 | 0.6 | 0.1170 | 0.44 ( 0.15, 1.26) | 0.44 ( 0.15, 1.27) | -0.01 (-0.02, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 12 | 1.3 | 938 | 5 | 0.5 | 0.0812 | 0.41 ( 0.14, 1.16) | 0.41 ( 0.14, 1.16) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 311 | 5 | 1.6 | 318 | 1 | 0.3 | 0.0952 | 0.20 ( 0.02, 1.66) | 0.19 ( 0.02, 1.66) | -0.01 (-0.03, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.5554 |
| Low, moderate or high | 1477 | 23 | 1.6 | 1548 | 10 | 0.6 | 0.0159 | 0.41 ( 0.20, 0.87) | 0.41 ( 0.19, 0.87) | -0.01 (-0.02, 0.00) | |
| Very high | 519 | 5 | 1.0 | 495 | 1 | 0.2 | 0.1141 | 0.21 ( 0.02, 1.79) | 0.21 ( 0.02, 1.79) | -0.01 (-0.02, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3170 |
| No | 411 | 6 | 1.5 | 410 | 4 | 1.0 | 0.5271 | 0.67 ( 0.19, 2.35) | 0.67 ( 0.19, 2.37) | 0.00 (-0.02, 0.01) | |
| Yes | 1590 | 22 | 1.4 | 1642 | 7 | 0.4 | 0.0039 | 0.31 ( 0.13, 0.72) | 0.31 ( 0.13, 0.72) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.4885 |
| No | 282 | 3 | 1.1 | 277 | 0 | 0 | 0.1369 | 0.15 (<0.01, 2.80) | 0.14 (<0.01, 2.80) | -0.01 (-0.02, 0.00) | |
| Yes | 1719 | 25 | 1.5 | 1775 | 11 | 0.6 | 0.0146 | 0.43 ( 0.21, 0.86) | 0.42 ( 0.21, 0.86) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.4631 |
| No | 229 | 5 | 2.2 | 250 | 1 | 0.4 | 0.0796 | 0.18 ( 0.02, 1.56) | 0.18 ( 0.02, 1.55) | -0.02 (-0.04, 0.00) | |
| Yes | 1772 | 23 | 1.3 | 1802 | 10 | 0.6 | 0.0202 | 0.43 ( 0.20, 0.90) | 0.42 ( 0.20, 0.89) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Decreased appetite

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 26 | 1.3 | 2052 | 17 | 0.8 | 0.1435 | 0.64 ( 0.35, 1.17) | 0.63 ( 0.34, 1.17) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypertriglyceridaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 21 | 1.0 | 2052 | 26 | 1.3 | 0.5177 | 1.21 ( 0.68, 2.14) | 1.21 ( 0.68, 2.16) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Dyslipidaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 23 | 1.1 | 2052 | 18 | 0.9 | 0.3865 | 0.76 ( 0.41, 1.41) | 0.76 ( 0.41, 1.41) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal impairment

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 198 | 9.9 | 2052 | 211 | 10.3 | 0.6821 | 1.04 ( 0.86, 1.25) | 1.04 ( 0.85, 1.28) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 117 | 5.8 | 2052 | 90 | 4.4 | 0.0346 | 0.75 | ( 0.57, 0.98) | 0.74 | ( 0.56, 0.98) | -0.01 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4120 |
| Male | 1065 | 65 | 6.1 | 1093 | 45 | 4.1 | 0.0360 | 0.67 | ( 0.47, 0.98) | 0.66 | ( 0.45, 0.98) | -0.02 | (-0.04, 0.00) | |
| Female | 936 | 52 | 5.6 | 959 | 45 | 4.7 | 0.3940 | 0.84 | ( 0.57, 1.25) | 0.84 | ( 0.56, 1.26) | -0.01 | (-0.03, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.4388 |
| <65 | 331 | 14 | 4.2 | 313 | 13 | 4.2 | 0.9615 | 0.98 | ( 0.47, 2.06) | 0.98 | ( 0.45, 2.12) | 0.00 | (-0.03, 0.03) | |
| >=65 | 1670 | 103 | 6.2 | 1739 | 77 | 4.4 | 0.0232 | 0.72 | ( 0.54, 0.96) | 0.70 | ( 0.52, 0.95) | -0.02 | (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | | 0.6311 |
| North America | 273 | 44 | 16.1 | 273 | 38 | 13.9 | 0.4723 | 0.86 | ( 0.58, 1.29) | 0.84 | ( 0.53, 1.35) | -0.02 | (-0.08, 0.04) | |
| Latin America | 511 | 24 | 4.7 | 504 | 20 | 4.0 | 0.5688 | 0.84 | ( 0.47, 1.51) | 0.84 | ( 0.46, 1.54) | -0.01 | (-0.03, 0.02) | |
| Europe | 865 | 30 | 3.5 | 894 | 18 | 2.0 | 0.0612 | 0.58 | ( 0.33, 1.03) | 0.57 | ( 0.32, 1.03) | -0.01 | (-0.03, 0.00) | |
| Asia | 231 | 9 | 3.9 | 248 | 4 | 1.6 | 0.1244 | 0.41 | ( 0.13, 1.33) | 0.40 | ( 0.12, 1.33) | -0.02 | (-0.05, 0.01) | |
| Other | 121 | 10 | 8.3 | 133 | 10 | 7.5 | 0.8256 | 0.91 | ( 0.39, 2.11) | 0.90 | ( 0.36, 2.25) | -0.01 | (-0.07, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4363 |
| Diabetic | 1045 | 77 | 7.4 | 1081 | 55 | 5.1 | 0.0294 | 0.69 | ( 0.49, 0.97) | 0.67 | ( 0.47, 0.96) | -0.02 | (-0.04, 0.00) | |
| Non-Diabetic | 956 | 40 | 4.2 | 971 | 35 | 3.6 | 0.5107 | 0.86 | ( 0.55, 1.34) | 0.86 | ( 0.54, 1.36) | -0.01 | (-0.02, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1113 |
| <30 | 1086 | 58 | 5.3 | 1094 | 34 | 3.1 | 0.0095 | 0.58 | ( 0.38, 0.88) | 0.57 | ( 0.37, 0.88) | -0.02 | (-0.04,-0.01) | |
| >=30 | 915 | 59 | 6.4 | 958 | 56 | 5.8 | 0.5871 | 0.91 | ( 0.64, 1.29) | 0.90 | ( 0.62, 1.31) | -0.01 | (-0.03, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3103 |
| <130 | 827 | 54 | 6.5 | 853 | 48 | 5.6 | 0.4387 | 0.86 | ( 0.59, 1.26) | 0.85 | ( 0.57, 1.27) | -0.01 | (-0.03, 0.01) | |
| >=130 | 1174 | 63 | 5.4 | 1199 | 42 | 3.5 | 0.0273 | 0.65 | ( 0.45, 0.96) | 0.64 | ( 0.43, 0.95) | -0.02 | (-0.04, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4071 |
| <75 | 935 | 67 | 7.2 | 934 | 56 | 6.0 | 0.3077 | 0.84 | ( 0.59, 1.18) | 0.83 | ( 0.57, 1.19) | -0.01 | (-0.03, 0.01) | |
| 75 to <85 | 657 | 31 | 4.7 | 703 | 25 | 3.6 | 0.2811 | 0.75 | ( 0.45, 1.26) | 0.74 | ( 0.43, 1.28) | -0.01 | (-0.03, 0.01) | |
| >=85 | 409 | 19 | 4.6 | 415 | 9 | 2.2 | 0.0498 | 0.47 | ( 0.21, 1.02) | 0.46 | ( 0.20, 1.02) | -0.02 | (-0.05, 0.00) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6575 |
| <30 | 161 | 19 | 11.8 | 148 | 17 | 11.5 | 0.9313 | 0.97 ( 0.53, 1.80) | 0.97 ( 0.48, 1.95) | 0.00 | (-0.07, 0.07) | |
| 30 to <45 | 550 | 41 | 7.5 | 564 | 32 | 5.7 | 0.2298 | 0.76 ( 0.49, 1.19) | 0.75 ( 0.46, 1.20) | -0.02 | (-0.05, 0.01) | |
| >=45 | 1289 | 57 | 4.4 | 1340 | 41 | 3.1 | 0.0653 | 0.69 ( 0.47, 1.03) | 0.68 ( 0.45, 1.03) | -0.01 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9779 |
| Normal (<30) | 764 | 36 | 4.7 | 787 | 29 | 3.7 | 0.3128 | 0.78 ( 0.48, 1.26) | 0.77 ( 0.47, 1.27) | -0.01 | (-0.03, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 59 | 6.4 | 938 | 44 | 4.7 | 0.1060 | 0.73 ( 0.50, 1.07) | 0.72 ( 0.48, 1.07) | -0.02 | (-0.04, 0.00) | |
| Macroalbuminuria (>300) | 311 | 22 | 7.1 | 318 | 17 | 5.3 | 0.3689 | 0.76 ( 0.41, 1.40) | 0.74 ( 0.39, 1.43) | -0.02 | (-0.06, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7892 |
| Low, moderate or high | 1477 | 67 | 4.5 | 1548 | 52 | 3.4 | 0.0960 | 0.74 ( 0.52, 1.06) | 0.73 ( 0.51, 1.06) | -0.01 | (-0.03, 0.00) | |
| Very high | 519 | 50 | 9.6 | 495 | 38 | 7.7 | 0.2685 | 0.80 ( 0.53, 1.19) | 0.78 ( 0.50, 1.21) | -0.02 | (-0.05, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7305 |
| No | 411 | 27 | 6.6 | 410 | 22 | 5.4 | 0.4667 | 0.82 ( 0.47, 1.41) | 0.81 ( 0.45, 1.44) | -0.01 | (-0.04, 0.02) | |
| Yes | 1590 | 90 | 5.7 | 1642 | 68 | 4.1 | 0.0453 | 0.73 ( 0.54, 0.99) | 0.72 ( 0.52, 0.99) | -0.02 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.7650 |
| No | 282 | 18 | 6.4 | 277 | 12 | 4.3 | 0.2820 | 0.68 ( 0.33, 1.38) | 0.66 ( 0.31, 1.41) | -0.02 | (-0.06, 0.02) | |
| Yes | 1719 | 99 | 5.8 | 1775 | 78 | 4.4 | 0.0659 | 0.76 ( 0.57, 1.02) | 0.75 ( 0.55, 1.02) | -0.01 | (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2457 |
| No | 229 | 11 | 4.8 | 250 | 5 | 2.0 | 0.0881 | 0.42 ( 0.15, 1.18) | 0.40 ( 0.14, 1.18) | -0.03 | (-0.06, 0.00) | |
| Yes | 1772 | 106 | 6.0 | 1802 | 85 | 4.7 | 0.0927 | 0.79 ( 0.60, 1.04) | 0.78 ( 0.58, 1.04) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 87 | 4.3 | 2052 | 76 | 3.7 | 0.2967 | 0.85 ( 0.63, 1.15) | 0.85 ( 0.62, 1.16) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Chronic kidney disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 83 | 4.1 | 2052 | 67 | 3.3 | 0.1366 | 0.79 ( 0.57, 1.08) | 0.78 ( 0.56, 1.08) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Microalbuminuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 32 | 1.6 | 2052 | 29 | 1.4 | 0.6269 | 0.88 ( 0.54, 1.46) | 0.88 ( 0.53, 1.46) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Haematuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 23 | 1.1 | 2052 | 23 | 1.1 | 0.9316 | 0.98 ( 0.55, 1.73) | 0.97 ( 0.55, 1.74) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 2001 | 144 | 7.2 | 2052 | 189 | 9.2 | 0.0196 | 1.28 | ( 1.04, 1.58) | 1.31 | ( 1.04, 1.64) | 0.02 | ( 0.00, 0.04) | |
| Sex | | | | | | | | | | | | | | 0.6337 |
| Male | 1065 | 79 | 7.4 | 1093 | 99 | 9.1 | 0.1662 | 1.22 | ( 0.92, 1.62) | 1.24 | ( 0.91, 1.69) | 0.02 | (-0.01, 0.04) | |
| Female | 936 | 65 | 6.9 | 959 | 90 | 9.4 | 0.0526 | 1.35 | (<1.00, 1.84) | 1.39 | ( 1.00, 1.94) | 0.02 | ( 0.00, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.4856 |
| <65 | 331 | 17 | 5.1 | 313 | 25 | 8.0 | 0.1430 | 1.56 | ( 0.86, 2.82) | 1.60 | ( 0.85, 3.03) | 0.03 | (-0.01, 0.07) | |
| >=65 | 1670 | 127 | 7.6 | 1739 | 164 | 9.4 | 0.0565 | 1.24 | ( 0.99, 1.55) | 1.27 | ( 0.99, 1.61) | 0.02 | ( 0.00, 0.04) | |
| Region | | | | | | | | | | | | | | 0.0973 |
| North America | 273 | 32 | 11.7 | 273 | 43 | 15.8 | 0.1714 | 1.34 | ( 0.88, 2.06) | 1.41 | ( 0.86, 2.30) | 0.04 | (-0.02, 0.10) | |
| Latin America | 511 | 25 | 4.9 | 504 | 41 | 8.1 | 0.0362 | 1.66 | ( 1.03, 2.69) | 1.72 | ( 1.03, 2.88) | 0.03 | ( 0.00, 0.06) | |
| Europe | 865 | 67 | 7.7 | 894 | 67 | 7.5 | 0.8426 | 0.97 | ( 0.70, 1.34) | 0.96 | ( 0.68, 1.37) | 0.00 | (-0.03, 0.02) | |
| Asia | 231 | 13 | 5.6 | 248 | 16 | 6.5 | 0.7056 | 1.15 | ( 0.56, 2.33) | 1.16 | ( 0.54, 2.46) | 0.01 | (-0.03, 0.05) | |
| Other | 121 | 7 | 5.8 | 133 | 22 | 16.5 | 0.0071 | 2.86 | ( 1.27, 6.45) | 3.23 | ( 1.33, 7.86) | 0.11 | ( 0.03, 0.18) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5007 |
| Diabetic | 1045 | 70 | 6.7 | 1081 | 86 | 8.0 | 0.2665 | 1.19 | ( 0.88, 1.61) | 1.20 | ( 0.87, 1.67) | 0.01 | (-0.01, 0.03) | |
| Non-Diabetic | 956 | 74 | 7.7 | 971 | 103 | 10.6 | 0.0294 | 1.37 | ( 1.03, 1.82) | 1.41 | ( 1.03, 1.93) | 0.03 | ( 0.00, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8704 |
| <30 | 1086 | 71 | 6.5 | 1094 | 93 | 8.5 | 0.0823 | 1.30 | ( 0.97, 1.75) | 1.33 | ( 0.96, 1.83) | 0.02 | ( 0.00, 0.04) | |
| >=30 | 915 | 73 | 8.0 | 958 | 96 | 10.0 | 0.1230 | 1.26 | ( 0.94, 1.68) | 1.28 | ( 0.93, 1.77) | 0.02 | (-0.01, 0.05) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6252 |
| <130 | 827 | 79 | 9.6 | 853 | 109 | 12.8 | 0.0360 | 1.34 | ( 1.02, 1.76) | 1.39 | ( 1.02, 1.89) | 0.03 | ( 0.00, 0.06) | |
| >=130 | 1174 | 65 | 5.5 | 1199 | 80 | 6.7 | 0.2482 | 1.21 | ( 0.88, 1.66) | 1.22 | ( 0.87, 1.71) | 0.01 | (-0.01, 0.03) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0184 |
| <75 | 935 | 73 | 7.8 | 934 | 108 | 11.6 | 0.0061 | 1.48 | ( 1.12, 1.97) | 1.54 | ( 1.13, 2.11) | 0.04 | ( 0.01, 0.06) | |
| 75 to <85 | 657 | 50 | 7.6 | 703 | 43 | 6.1 | 0.2754 | 0.80 | ( 0.54, 1.19) | 0.79 | ( 0.52, 1.21) | -0.01 | (-0.04, 0.01) | |
| >=85 | 409 | 21 | 5.1 | 415 | 38 | 9.2 | 0.0252 | 1.78 | ( 1.07, 2.99) | 1.86 | ( 1.07, 3.23) | 0.04 | ( 0.01, 0.08) | |

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MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Vascular disorders
Preferred term: Hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.6322 |
| <30 | 161 | 13 | 8.1 | 148 | 18 | 12.2 | 0.2322 | 1.51 ( 0.76, | 2.97) | 1.58 ( 0.74, | 3.34) | 0.04 (-0.03, 0.11) | |
| 30 to <45 | 550 | 49 | 8.9 | 564 | 56 | 9.9 | 0.5602 | 1.11 ( 0.77, | 1.61) | 1.13 ( 0.75, | 1.69) | 0.01 (-0.02, 0.04) | |
| >=45 | 1289 | 82 | 6.4 | 1340 | 115 | 8.6 | 0.0306 | 1.35 ( 1.03, | 1.77) | 1.38 ( 1.03, | 1.85) | 0.02 ( 0.00, 0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.7777 |
| Normal (<30) | 764 | 65 | 8.5 | 787 | 93 | 11.8 | 0.0312 | 1.39 ( 1.03, | 1.88) | 1.44 ( 1.03, | 2.01) | 0.03 ( 0.00, 0.06) | |
| Microalbuminuria (30 to <=300) | 921 | 63 | 6.8 | 938 | 77 | 8.2 | 0.2636 | 1.20 ( 0.87, | 1.65) | 1.22 ( 0.86, | 1.72) | 0.01 (-0.01, 0.04) | |
| Macroalbuminuria (>300) | 311 | 15 | 4.8 | 318 | 18 | 5.7 | 0.6377 | 1.17 ( 0.60, | 2.29) | 1.18 ( 0.59, | 2.39) | 0.01 (-0.03, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.5104 |
| Low, moderate or high | 1477 | 106 | 7.2 | 1548 | 137 | 8.9 | 0.0905 | 1.23 ( 0.97, | 1.57) | 1.26 ( 0.96, | 1.64) | 0.02 ( 0.00, 0.04) | |
| Very high | 519 | 37 | 7.1 | 495 | 51 | 10.3 | 0.0727 | 1.45 ( 0.96, | 2.17) | 1.50 ( 0.96, | 2.33) | 0.03 ( 0.00, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.1612 |
| No | 411 | 32 | 7.8 | 410 | 30 | 7.3 | 0.7993 | 0.94 ( 0.58, | 1.52) | 0.94 ( 0.56, | 1.57) | 0.00 (-0.04, 0.03) | |
| Yes | 1590 | 112 | 7.0 | 1642 | 159 | 9.7 | 0.0068 | 1.37 ( 1.09, | 1.73) | 1.41 ( 1.10, | 1.82) | 0.03 ( 0.01, 0.05) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.2451 |
| No | 282 | 14 | 5.0 | 277 | 25 | 9.0 | 0.0595 | 1.82 ( 0.97, | 3.42) | 1.90 ( 0.97, | 3.74) | 0.04 ( 0.00, 0.08) | |
| Yes | 1719 | 130 | 7.6 | 1775 | 164 | 9.2 | 0.0742 | 1.22 ( 0.98, | 1.52) | 1.24 ( 0.98, | 1.58) | 0.02 ( 0.00, 0.04) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.8967 |
| No | 229 | 6 | 2.6 | 250 | 9 | 3.6 | 0.5385 | 1.37 ( 0.50, | 3.80) | 1.39 ( 0.49, | 3.96) | 0.01 (-0.02, 0.04) | |
| Yes | 1772 | 138 | 7.8 | 1802 | 180 | 10.0 | 0.0208 | 1.28 ( 1.04, | 1.59) | 1.31 ( 1.04, | 1.66) | 0.02 ( 0.00, 0.04) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypertension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 179 | 8.9 | 2052 | 184 | 9.0 | 0.9810 | 1.00 ( 0.82, 1.22) | 1.00 ( 0.81, 1.24) | 0.00 (-0.02, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Vascular disorders
Preferred term: Peripheral arterial occlusive disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 32 | 1.6 | 2052 | 29 | 1.4 | 0.6269 | 0.88 ( 0.54, 1.46) | 0.88 ( 0.53, 1.46) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypertensive crisis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 25 | 1.2 | 2052 | 16 | 0.8 | 0.1352 | 0.62 ( 0.33, 1.17) | 0.62 ( 0.33, 1.17) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Haematoma

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 20 | 1.0 | 2052 | 21 | 1.0 | 0.9394 | 1.02 ( 0.56, 1.88) | 1.02 ( 0.55, 1.90) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Diarrhoea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 92 | 4.6 | 2052 | 104 | 5.1 | 0.4851 | 1.10 ( 0.84, 1.45) | 1.11 ( 0.83, 1.48) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Gastrointestinal disorders
Preferred term: Constipation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 66 | 3.3 | 2052 | 84 | 4.1 | 0.1800 | 1.24 ( 0.90, 1.70) | 1.25 ( 0.90, 1.74) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Gastrointestinal disorders
Preferred term: Nausea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 38 | 1.9 | 2052 | 55 | 2.7 | 0.0968 | 1.41 ( 0.94, 2.12) | 1.42 ( 0.94, 2.16) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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System organ class: Gastrointestinal disorders
Preferred term: Vomiting

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 35 | 1.7 | 2052 | 31 | 1.5 | 0.5488 | 0.86 ( 0.53, 1.40) | 0.86 ( 0.53, 1.40) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Gastritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 29 | 1.4 | 2052 | 30 | 1.5 | 0.9730 | 1.01 ( 0.61, 1.67) | 1.01 ( 0.60, 1.69) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Abdominal pain upper

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 23 | 1.1 | 2052 | 26 | 1.3 | 0.7319 | 1.10 ( 0.63, 1.93) | 1.10 ( 0.63, 1.94) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Abdominal pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 17 | 0.8 | 2052 | 25 | 1.2 | 0.2465 | 1.43 ( 0.78, 2.65) | 1.44 ( 0.77, 2.67) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Dyspepsia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 21 | 1.0 | 2052 | 25 | 1.2 | 0.6119 | 1.16 ( 0.65, 2.07) | 1.16 ( 0.65, 2.08) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Haemorrhoids

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 16 | 0.8 | 2052 | 24 | 1.2 | 0.2335 | 1.46 ( 0.78, 2.75) | 1.47 ( 0.78, 2.77) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Gastrooesophageal reflux disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 16 | 0.8 | 2052 | 23 | 1.1 | 0.2949 | 1.40 ( 0.74, 2.65) | 1.41 ( 0.74, 2.67) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Back pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 88 | 4.4 | 2052 | 84 | 4.1 | 0.6310 | 0.93 ( 0.69, 1.25) | 0.93 ( 0.68, 1.26) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Arthralgia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 81 | 4.0 | 2052 | 90 | 4.4 | 0.5925 | 1.08 ( 0.81, | 1.45) | 1.09 ( 0.80, | 1.48) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Pain in extremity

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 68 | 3.4 | 2052 | 44 | 2.1 | 0.0149 | 0.63 ( 0.43, | 0.92) | 0.62 ( 0.42, | 0.91) | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | 0.9476 |
| Male | 1065 | 32 | 3.0 | 1093 | 21 | 1.9 | 0.1040 | 0.64 ( 0.37, | 1.10) | 0.63 ( 0.36, | 1.10) | -0.01 (-0.02, 0.00) | |
| Female | 936 | 36 | 3.8 | 959 | 23 | 2.4 | 0.0696 | 0.62 ( 0.37, | 1.04) | 0.61 ( 0.36, | 1.04) | -0.01 (-0.03, 0.00) | |
| Age [years] | | | | | | | | | | | | | 0.6634 |
| <65 | 331 | 14 | 4.2 | 313 | 7 | 2.2 | 0.1546 | 0.53 ( 0.22, | 1.29) | 0.52 ( 0.21, | 1.30) | -0.02 (-0.05, 0.01) | |
| >=65 | 1670 | 54 | 3.2 | 1739 | 37 | 2.1 | 0.0452 | 0.66 ( 0.44, | 0.99) | 0.65 ( 0.43, | 0.99) | -0.01 (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | 0.4347 |
| North America | 273 | 23 | 8.4 | 273 | 11 | 4.0 | 0.0336 | 0.48 ( 0.24, | 0.96) | 0.46 ( 0.22, | 0.96) | -0.04 (-0.08, 0.00) | |
| Latin America | 511 | 13 | 2.5 | 504 | 15 | 3.0 | 0.6743 | 1.17 ( 0.56, | 2.43) | 1.18 ( 0.55, | 2.50) | 0.00 (-0.02, 0.02) | |
| Europe | 865 | 15 | 1.7 | 894 | 9 | 1.0 | 0.1886 | 0.58 ( 0.26, | 1.32) | 0.58 ( 0.25, | 1.32) | -0.01 (-0.02, 0.00) | |
| Asia | 231 | 12 | 5.2 | 248 | 6 | 2.4 | 0.1105 | 0.47 ( 0.18, | 1.22) | 0.45 ( 0.17, | 1.23) | -0.03 (-0.06, 0.01) | |
| Other | 121 | 5 | 4.1 | 133 | 3 | 2.3 | 0.3924 | 0.55 ( 0.13, | 2.24) | 0.54 ( 0.13, | 2.29) | -0.02 (-0.06, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.3292 |
| Diabetic | 1045 | 40 | 3.8 | 1081 | 22 | 2.0 | 0.0141 | 0.53 ( 0.32, | 0.89) | 0.52 ( 0.31, | 0.88) | -0.02 (-0.03, 0.00) | |
| Non-Diabetic | 956 | 28 | 2.9 | 971 | 22 | 2.3 | 0.3599 | 0.77 ( 0.45, | 1.34) | 0.77 ( 0.44, | 1.35) | -0.01 (-0.02, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.8358 |
| <30 | 1086 | 36 | 3.3 | 1094 | 22 | 2.0 | 0.0585 | 0.61 ( 0.36, | 1.02) | 0.60 ( 0.35, | 1.02) | -0.01 (-0.03, 0.00) | |
| >=30 | 915 | 32 | 3.5 | 958 | 22 | 2.3 | 0.1205 | 0.66 ( 0.38, | 1.12) | 0.65 ( 0.37, | 1.12) | -0.01 (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.3247 |
| <130 | 827 | 23 | 2.8 | 853 | 19 | 2.2 | 0.4674 | 0.80 ( 0.44, | 1.46) | 0.80 ( 0.43, | 1.47) | -0.01 (-0.02, 0.01) | |
| >=130 | 1174 | 45 | 3.8 | 1199 | 25 | 2.1 | 0.0119 | 0.54 ( 0.34, | 0.88) | 0.53 ( 0.33, | 0.88) | -0.02 (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.0653 |
| <75 | 935 | 32 | 3.4 | 934 | 27 | 2.9 | 0.5110 | 0.84 ( 0.51, | 1.40) | 0.84 ( 0.50, | 1.41) | -0.01 (-0.02, 0.01) | |
| 75 to <85 | 657 | 17 | 2.6 | 703 | 13 | 1.8 | 0.3543 | 0.71 ( 0.35, | 1.46) | 0.71 ( 0.34, | 1.47) | -0.01 (-0.02, 0.01) | |
| >=85 | 409 | 19 | 4.6 | 415 | 4 | 1.0 | 0.0013 | 0.21 ( 0.07, | 0.60) | 0.20 ( 0.07, | 0.59) | -0.04 (-0.06,-0.01) | |

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MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Pain in extremity

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.9573 |
| <30 | 161 | 5 | 3.1 | 148 | 3 | 2.0 | 0.5509 | 0.65 ( 0.16, | 2.68) | 0.65 ( 0.15, | 2.75) | -0.01 (-0.05, 0.02) | |
| 30 to <45 | 550 | 20 | 3.6 | 564 | 14 | 2.5 | 0.2629 | 0.68 ( 0.35, | 1.34) | 0.67 ( 0.34, | 1.35) | -0.01 (-0.03, 0.01) | |
| >=45 | 1289 | 43 | 3.3 | 1340 | 27 | 2.0 | 0.0354 | 0.60 ( 0.38, | 0.97) | 0.60 ( 0.37, | 0.97) | -0.01 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.2503 |
| Normal (<30) | 764 | 23 | 3.0 | 787 | 21 | 2.7 | 0.6850 | 0.89 ( 0.49, | 1.59) | 0.88 ( 0.48, | 1.61) | 0.00 (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 30 | 3.3 | 938 | 13 | 1.4 | 0.0073 | 0.43 ( 0.22, | 0.81) | 0.42 ( 0.22, | 0.81) | -0.02 (-0.03,-0.01) | |
| Macroalbuminuria (>300) | 311 | 15 | 4.8 | 318 | 9 | 2.8 | 0.1921 | 0.59 ( 0.26, | 1.32) | 0.57 ( 0.25, | 1.33) | -0.02 (-0.05, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.9127 |
| Low, moderate or high | 1477 | 50 | 3.4 | 1548 | 32 | 2.1 | 0.0257 | 0.61 ( 0.39, | 0.95) | 0.60 ( 0.38, | 0.94) | -0.01 (-0.02, 0.00) | |
| Very high | 519 | 18 | 3.5 | 495 | 11 | 2.2 | 0.2341 | 0.64 ( 0.31, | 1.34) | 0.63 ( 0.30, | 1.35) | -0.01 (-0.03, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.2028 |
| No | 411 | 20 | 4.9 | 410 | 8 | 2.0 | 0.0214 | 0.40 ( 0.18, | 0.90) | 0.39 ( 0.17, | 0.89) | -0.03 (-0.05, 0.00) | |
| Yes | 1590 | 48 | 3.0 | 1642 | 36 | 2.2 | 0.1399 | 0.73 ( 0.47, | 1.11) | 0.72 ( 0.46, | 1.12) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.5535 |
| No | 282 | 9 | 3.2 | 277 | 4 | 1.4 | 0.1705 | 0.45 ( 0.14, | 1.45) | 0.44 ( 0.14, | 1.46) | -0.02 (-0.04, 0.01) | |
| Yes | 1719 | 59 | 3.4 | 1775 | 40 | 2.3 | 0.0358 | 0.66 ( 0.44, | 0.98) | 0.65 ( 0.43, | 0.97) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.4960 |
| No | 229 | 5 | 2.2 | 250 | 2 | 0.8 | 0.2075 | 0.37 ( 0.07, | 1.87) | 0.36 ( 0.07, | 1.88) | -0.01 (-0.04, 0.01) | |
| Yes | 1772 | 63 | 3.6 | 1802 | 42 | 2.3 | 0.0302 | 0.66 ( 0.45, | 0.96) | 0.65 ( 0.44, | 0.96) | -0.01 (-0.02, 0.00) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Osteoarthritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 62 | 3.1 | 2052 | 55 | 2.7 | 0.4267 | 0.87 ( 0.60, 1.24) | 0.86 ( 0.60, 1.24) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Muscle spasms

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 33 | 1.6 | 2052 | 30 | 1.5 | 0.6301 | 0.89 ( 0.54, 1.45) | 0.88 ( 0.54, 1.46) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Nervous system disorders
Preferred term: Dizziness

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 77 | 3.8 | 2052 | 93 | 4.5 | 0.2774 | 1.18 ( 0.88, | 1.58) | 1.19 ( 0.87, | 1.61) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Nervous system disorders
Preferred term: Headache

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 52 | 2.6 | 2052 | 47 | 2.3 | 0.5250 | 0.88 ( 0.60, 1.30) | 0.88 ( 0.59, 1.31) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Syncope

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 44 | 2.2 | 2052 | 53 | 2.6 | 0.4240 | 1.17 ( 0.79, 1.74) | 1.18 ( 0.79, 1.77) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 38 | 1.9 | 2052 | 33 | 1.6 | 0.4804 | 0.85 ( 0.53, | 1.34) | 0.84 ( 0.53, | 1.35) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Cerebrovascular accident

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 18 | 0.9 | 2052 | 22 | 1.1 | 0.5784 | 1.19 ( 0.64, 2.22) | 1.19 ( 0.64, 2.23) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Sciatica

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 14 | 0.7 | 2052 | 21 | 1.0 | 0.2654 | 1.46 ( 0.75, 2.87) | 1.47 ( 0.74, 2.89) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Chronic obstructive pulmonary disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 81 | 4.0 | 2052 | 56 | 2.7 | 0.0202 | 0.67 ( 0.48, | 0.94) | 0.67 ( 0.47, | 0.94) | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | 0.2129 |
| Male | 1065 | 45 | 4.2 | 1093 | 37 | 3.4 | 0.3074 | 0.80 ( 0.52, | 1.23) | 0.79 ( 0.51, | 1.24) | -0.01 (-0.02, 0.01) | |
| Female | 936 | 36 | 3.8 | 959 | 19 | 2.0 | 0.0156 | 0.52 ( 0.30, | 0.89) | 0.51 ( 0.29, | 0.89) | -0.02 (-0.03, 0.00) | |
| Age [years] | | | | | | | | | | | | | 0.0535 |
| <65 | 331 | 11 | 3.3 | 313 | 14 | 4.5 | 0.4503 | 1.35 ( 0.62, | 2.92) | 1.36 ( 0.61, | 3.05) | 0.01 (-0.02, 0.04) | |
| >=65 | 1670 | 70 | 4.2 | 1739 | 42 | 2.4 | 0.0036 | 0.58 ( 0.40, | 0.84) | 0.57 ( 0.38, | 0.83) | -0.02 (-0.03,-0.01) | |
| Region | | | | | | | | | | | | | 0.7656 |
| North America | 273 | 28 | 10.3 | 273 | 14 | 5.1 | 0.0245 | 0.50 ( 0.27, | 0.93) | 0.47 ( 0.24, | 0.92) | -0.05 (-0.10,-0.01) | |
| Latin America | 511 | 15 | 2.9 | 504 | 10 | 2.0 | 0.3282 | 0.68 ( 0.31, | 1.49) | 0.67 ( 0.30, | 1.50) | -0.01 (-0.03, 0.01) | |
| Europe | 865 | 30 | 3.5 | 894 | 23 | 2.6 | 0.2720 | 0.74 ( 0.43, | 1.27) | 0.73 ( 0.42, | 1.28) | -0.01 (-0.02, 0.01) | |
| Asia | 231 | 3 | 1.3 | 248 | 3 | 1.2 | 0.9302 | 0.93 ( 0.19, | 4.57) | 0.93 ( 0.19, | 4.66) | 0.00 (-0.02, 0.02) | |
| Other | 121 | 5 | 4.1 | 133 | 6 | 4.5 | 0.8822 | 1.09 ( 0.34, | 3.49) | 1.10 ( 0.33, | 3.69) | 0.00 (-0.05, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.7298 |
| Diabetic | 1045 | 45 | 4.3 | 1081 | 33 | 3.1 | 0.1243 | 0.71 ( 0.46, | 1.10) | 0.70 ( 0.44, | 1.11) | -0.01 (-0.03, 0.00) | |
| Non-Diabetic | 956 | 36 | 3.8 | 971 | 23 | 2.4 | 0.0751 | 0.63 ( 0.38, | 1.05) | 0.62 ( 0.36, | 1.05) | -0.01 (-0.03, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.6111 |
| <30 | 1086 | 39 | 3.6 | 1094 | 24 | 2.2 | 0.0515 | 0.61 ( 0.37, | 1.01) | 0.60 ( 0.36, | 1.01) | -0.01 (-0.03, 0.00) | |
| >=30 | 915 | 42 | 4.6 | 958 | 32 | 3.3 | 0.1651 | 0.73 ( 0.46, | 1.14) | 0.72 ( 0.45, | 1.15) | -0.01 (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.5159 |
| <130 | 827 | 39 | 4.7 | 853 | 24 | 2.8 | 0.0402 | 0.60 ( 0.36, | 0.98) | 0.58 ( 0.35, | 0.98) | -0.02 (-0.04, 0.00) | |
| >=130 | 1174 | 42 | 3.6 | 1199 | 32 | 2.7 | 0.2030 | 0.75 ( 0.47, | 1.17) | 0.74 ( 0.46, | 1.18) | -0.01 (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.2089 |
| <75 | 935 | 48 | 5.1 | 934 | 24 | 2.6 | 0.0040 | 0.50 ( 0.31, | 0.81) | 0.49 ( 0.30, | 0.80) | -0.03 (-0.04,-0.01) | |
| 75 to <85 | 657 | 23 | 3.5 | 703 | 22 | 3.1 | 0.7020 | 0.89 ( 0.50, | 1.59) | 0.89 ( 0.49, | 1.61) | 0.00 (-0.02, 0.02) | |
| >=85 | 409 | 10 | 2.4 | 415 | 10 | 2.4 | 0.9737 | 0.99 ( 0.41, | 2.34) | 0.99 ( 0.41, | 2.39) | 0.00 (-0.02, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Chronic obstructive pulmonary disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.3155 |
| <30 | 161 | 7 | 4.3 | 148 | 3 | 2.0 | 0.2495 | 0.47 ( 0.12, | 1.77) | 0.46 ( 0.12, | 1.79) | -0.02 (-0.06, 0.02) | |
| 30 to <45 | 550 | 33 | 6.0 | 564 | 17 | 3.0 | 0.0161 | 0.50 ( 0.28, | 0.89) | 0.49 ( 0.27, | 0.88) | -0.03 (-0.05,-0.01) | |
| >=45 | 1289 | 41 | 3.2 | 1340 | 36 | 2.7 | 0.4525 | 0.84 ( 0.54, | 1.31) | 0.84 ( 0.53, | 1.32) | 0.00 (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.5326 |
| Normal (<30) | 764 | 38 | 5.0 | 787 | 22 | 2.8 | 0.0261 | 0.56 ( 0.34, | 0.94) | 0.55 ( 0.32, | 0.94) | -0.02 (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 32 | 3.5 | 938 | 22 | 2.3 | 0.1473 | 0.68 ( 0.40, | 1.15) | 0.67 ( 0.38, | 1.16) | -0.01 (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 311 | 11 | 3.5 | 318 | 11 | 3.5 | 0.9576 | 0.98 ( 0.43, | 2.22) | 0.98 ( 0.42, | 2.29) | 0.00 (-0.03, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.9633 |
| Low, moderate or high | 1477 | 54 | 3.7 | 1548 | 38 | 2.5 | 0.0545 | 0.67 ( 0.45, | 1.01) | 0.66 ( 0.44, | 1.01) | -0.01 (-0.02, 0.00) | |
| Very high | 519 | 27 | 5.2 | 495 | 17 | 3.4 | 0.1672 | 0.66 ( 0.36, | 1.20) | 0.65 ( 0.35, | 1.20) | -0.02 (-0.04, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.1375 |
| No | 411 | 15 | 3.6 | 410 | 16 | 3.9 | 0.8493 | 1.07 ( 0.54, | 2.13) | 1.07 ( 0.52, | 2.20) | 0.00 (-0.02, 0.03) | |
| Yes | 1590 | 66 | 4.2 | 1642 | 40 | 2.4 | 0.0062 | 0.59 ( 0.40, | 0.86) | 0.58 ( 0.39, | 0.86) | -0.02 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.3397 |
| No | 282 | 9 | 3.2 | 277 | 9 | 3.2 | 0.9692 | 1.02 ( 0.41, | 2.53) | 1.02 ( 0.40, | 2.61) | 0.00 (-0.03, 0.03) | |
| Yes | 1719 | 72 | 4.2 | 1775 | 47 | 2.6 | 0.0121 | 0.63 ( 0.44, | 0.91) | 0.62 ( 0.43, | 0.90) | -0.02 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.9847 |
| No | 229 | 4 | 1.7 | 250 | 3 | 1.2 | 0.6184 | 0.69 ( 0.16, | 3.04) | 0.68 ( 0.15, | 3.09) | -0.01 (-0.03, 0.02) | |
| Yes | 1772 | 77 | 4.3 | 1802 | 53 | 2.9 | 0.0250 | 0.68 ( 0.48, | 0.95) | 0.67 ( 0.47, | 0.95) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Dyspnoea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 71 | 3.5 | 2052 | 75 | 3.7 | 0.8553 | 1.03 ( 0.75, 1.42) | 1.03 ( 0.74, 1.44) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Cough

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 43 | 2.1 | 2052 | 49 | 2.4 | 0.6095 | 1.11 ( 0.74, 1.67) | 1.11 ( 0.74, 1.69) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Epistaxis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 42 | 2.1 | 2052 | 41 | 2.0 | 0.8206 | 0.95 ( 0.62, 1.46) | 0.95 ( 0.62, 1.47) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Asthma

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 27 | 1.3 | 2052 | 15 | 0.7 | 0.0520 | 0.54 ( 0.29, 1.02) | 0.54 ( 0.29, 1.02) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Pleural effusion

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 18 | 0.9 | 2052 | 27 | 1.3 | 0.2061 | 1.46 ( 0.81, 2.65) | 1.47 ( 0.81, 2.68) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Oedema peripheral

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 72 | 3.6 | 2052 | 76 | 3.7 | 0.8579 | 1.03 ( 0.75, 1.41) | 1.03 ( 0.74, 1.43) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 55 | 2.7 | 2052 | 69 | 3.4 | 0.2565 | 1.22 ( 0.86, 1.73) | 1.23 ( 0.86, 1.76) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: General disorders and administration site conditions
Preferred term: Non-cardiac chest pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 42 | 2.1 | 2052 | 44 | 2.1 | 0.9203 | 1.02 ( 0.67, 1.55) | 1.02 ( 0.67, 1.57) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Fatigue

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 35 | 1.7 | 2052 | 42 | 2.0 | 0.4877 | 1.17 ( 0.75, 1.82) | 1.17 ( 0.75, 1.85) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Chest pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 27 | 1.3 | 2052 | 27 | 1.3 | 0.9258 | 0.98 ( 0.57, 1.66) | 0.97 ( 0.57, 1.67) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Asthenia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 24 | 1.2 | 2052 | 27 | 1.3 | 0.7396 | 1.10 ( 0.64, 1.89) | 1.10 ( 0.63, 1.91) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 194 | 9.7 | 2052 | 197 | 9.6 | 0.9186 | 0.99 ( 0.82, 1.20) | 0.99 ( 0.80, 1.22) | 0.00 (-0.02, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Contusion

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 49 | 2.4 | 2052 | 55 | 2.7 | 0.6412 | 1.09 ( 0.75, 1.60) | 1.10 ( 0.74, 1.62) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Skin laceration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 18 | 0.9 | 2052 | 31 | 1.5 | 0.0751 | 1.68 ( 0.94, 2.99) | 1.69 ( 0.94, 3.03) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Limb injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 24 | 1.2 | 2052 | 27 | 1.3 | 0.7396 | 1.10 ( 0.64, 1.89) | 1.10 ( 0.63, 1.91) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 172 | 8.6 | 2052 | 132 | 6.4 | 0.0090 | 0.75 ( 0.60, 0.93) | | 0.73 ( 0.58, 0.93) | | -0.02 (-0.04,-0.01) | |
| Sex | | | | | | | | | | | | | 0.8376 |
| Male | 1065 | 97 | 9.1 | 1093 | 73 | 6.7 | 0.0362 | 0.73 ( 0.55, 0.98) | | 0.71 ( 0.52, 0.98) | | -0.02 (-0.05, 0.00) | |
| Female | 936 | 75 | 8.0 | 959 | 59 | 6.2 | 0.1142 | 0.77 ( 0.55, 1.07) | | 0.75 ( 0.53, 1.07) | | -0.02 (-0.04, 0.00) | |
| Age [years] | | | | | | | | | | | | | 0.2863 |
| <65 | 331 | 26 | 7.9 | 313 | 24 | 7.7 | 0.9293 | 0.98 ( 0.57, 1.66) | | 0.97 ( 0.55, 1.74) | | 0.00 (-0.04, 0.04) | |
| >=65 | 1670 | 146 | 8.7 | 1739 | 108 | 6.2 | 0.0049 | 0.71 ( 0.56, 0.90) | | 0.69 ( 0.53, 0.89) | | -0.03 (-0.04,-0.01) | |
| Region | | | | | | | | | | | | | 0.1820 |
| North America | 273 | 27 | 9.9 | 273 | 13 | 4.8 | 0.0215 | 0.48 ( 0.25, 0.91) | | 0.46 ( 0.23, 0.90) | | -0.05 (-0.09,-0.01) | |
| Latin America | 511 | 43 | 8.4 | 504 | 38 | 7.5 | 0.6069 | 0.90 ( 0.59, 1.36) | | 0.89 ( 0.56, 1.40) | | -0.01 (-0.04, 0.02) | |
| Europe | 865 | 68 | 7.9 | 894 | 46 | 5.1 | 0.0207 | 0.65 ( 0.46, 0.94) | | 0.64 ( 0.43, 0.94) | | -0.03 (-0.05, 0.00) | |
| Asia | 231 | 19 | 8.2 | 248 | 25 | 10.1 | 0.4823 | 1.23 ( 0.69, 2.16) | | 1.25 ( 0.67, 2.34) | | 0.02 (-0.03, 0.07) | |
| Other | 121 | 15 | 12.4 | 133 | 10 | 7.5 | 0.1924 | 0.61 ( 0.28, 1.30) | | 0.57 ( 0.25, 1.33) | | -0.05 (-0.12, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.0131 |
| Diabetic | 1045 | 89 | 8.5 | 1081 | 87 | 8.0 | 0.6950 | 0.94 ( 0.71, 1.25) | | 0.94 ( 0.69, 1.28) | | 0.00 (-0.03, 0.02) | |
| Non-Diabetic | 956 | 83 | 8.7 | 971 | 45 | 4.6 | 0.0004 | 0.53 ( 0.38, 0.76) | | 0.51 ( 0.35, 0.74) | | -0.04 (-0.06,-0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.1995 |
| <30 | 1086 | 95 | 8.7 | 1094 | 81 | 7.4 | 0.2496 | 0.85 ( 0.64, 1.12) | | 0.83 ( 0.61, 1.14) | | -0.01 (-0.04, 0.01) | |
| >=30 | 915 | 77 | 8.4 | 958 | 51 | 5.3 | 0.0080 | 0.63 ( 0.45, 0.89) | | 0.61 ( 0.42, 0.88) | | -0.03 (-0.05,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.4809 |
| <130 | 827 | 74 | 8.9 | 853 | 52 | 6.1 | 0.0265 | 0.68 ( 0.48, 0.96) | | 0.66 ( 0.46, 0.95) | | -0.03 (-0.05, 0.00) | |
| >=130 | 1174 | 98 | 8.3 | 1199 | 80 | 6.7 | 0.1214 | 0.80 ( 0.60, 1.06) | | 0.78 ( 0.58, 1.07) | | -0.02 (-0.04, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.3938 |
| <75 | 935 | 98 | 10.5 | 934 | 65 | 7.0 | 0.0070 | 0.66 ( 0.49, 0.90) | | 0.64 ( 0.46, 0.89) | | -0.04 (-0.06,-0.01) | |
| 75 to <85 | 657 | 47 | 7.2 | 703 | 47 | 6.7 | 0.7338 | 0.93 ( 0.63, 1.38) | | 0.93 ( 0.61, 1.41) | | 0.00 (-0.03, 0.02) | |
| >=85 | 409 | 27 | 6.6 | 415 | 20 | 4.8 | 0.2701 | 0.73 ( 0.42, 1.28) | | 0.72 ( 0.40, 1.30) | | -0.02 (-0.05, 0.01) | |

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MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.5949 |
| <30 | 161 | 26 | 16.1 | 148 | 23 | 15.5 | 0.8837 | 0.96 ( 0.58, | 1.61) | 0.96 ( 0.52, | 1.76) | -0.01 (-0.09, 0.08) | |
| 30 to <45 | 550 | 56 | 10.2 | 564 | 40 | 7.1 | 0.0662 | 0.70 ( 0.47, | 1.03) | 0.67 ( 0.44, | 1.03) | -0.03 (-0.06, 0.00) | |
| >=45 | 1289 | 90 | 7.0 | 1340 | 69 | 5.1 | 0.0487 | 0.74 ( 0.54, | <1.00) | 0.72 ( 0.52, | 1.00) | -0.02 (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.1856 |
| Normal (<30) | 764 | 58 | 7.6 | 787 | 43 | 5.5 | 0.0895 | 0.72 ( 0.49, | 1.05) | 0.70 ( 0.47, | 1.06) | -0.02 (-0.05, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 80 | 8.7 | 938 | 52 | 5.5 | 0.0083 | 0.64 ( 0.46, | 0.89) | 0.62 ( 0.43, | 0.89) | -0.03 (-0.05,-0.01) | |
| Macroalbuminuria (>300) | 311 | 34 | 10.9 | 318 | 37 | 11.6 | 0.7807 | 1.06 ( 0.69, | 1.65) | 1.07 ( 0.65, | 1.76) | 0.01 (-0.04, 0.06) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.6662 |
| Low, moderate or high | 1477 | 107 | 7.2 | 1548 | 82 | 5.3 | 0.0270 | 0.73 ( 0.55, | 0.97) | 0.72 ( 0.53, | 0.96) | -0.02 (-0.04, 0.00) | |
| Very high | 519 | 65 | 12.5 | 495 | 50 | 10.1 | 0.2239 | 0.81 ( 0.57, | 1.14) | 0.78 ( 0.53, | 1.16) | -0.02 (-0.06, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.2855 |
| No | 411 | 38 | 9.2 | 410 | 35 | 8.5 | 0.7211 | 0.92 ( 0.60, | 1.43) | 0.92 ( 0.57, | 1.48) | -0.01 (-0.05, 0.03) | |
| Yes | 1590 | 134 | 8.4 | 1642 | 97 | 5.9 | 0.0054 | 0.70 ( 0.54, | 0.90) | 0.68 ( 0.52, | 0.89) | -0.03 (-0.04,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.8250 |
| No | 282 | 26 | 9.2 | 277 | 18 | 6.5 | 0.2322 | 0.70 ( 0.40, | 1.26) | 0.68 ( 0.37, | 1.28) | -0.03 (-0.07, 0.02) | |
| Yes | 1719 | 146 | 8.5 | 1775 | 114 | 6.4 | 0.0197 | 0.76 ( 0.60, | 0.96) | 0.74 ( 0.57, | 0.95) | -0.02 (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.2378 |
| No | 229 | 12 | 5.2 | 250 | 15 | 6.0 | 0.7187 | 1.15 ( 0.55, | 2.39) | 1.15 ( 0.53, | 2.52) | 0.01 (-0.03, 0.05) | |
| Yes | 1772 | 160 | 9.0 | 1802 | 117 | 6.5 | 0.0046 | 0.72 ( 0.57, | 0.90) | 0.70 ( 0.55, | 0.90) | -0.03 (-0.04,-0.01) | |

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MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Iron deficiency anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 42 | 2.1 | 2052 | 24 | 1.2 | 0.0194 | 0.56 ( 0.34, | 0.92) | 0.55 ( 0.33, | 0.91) | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | 0.0491 |
| Male | 1065 | 28 | 2.6 | 1093 | 10 | 0.9 | 0.0025 | 0.35 ( 0.17, | 0.71) | 0.34 ( 0.17, | 0.71) | -0.02 (-0.03,-0.01) | |
| Female | 936 | 14 | 1.5 | 959 | 14 | 1.5 | 0.9484 | 0.98 ( 0.47, | 2.04) | 0.98 ( 0.46, | 2.06) | 0.00 (-0.01, 0.01) | |
| Age [years] | | | | | | | | | | | | | 0.7316 |
| <65 | 331 | 5 | 1.5 | 313 | 2 | 0.6 | 0.2863 | 0.42 ( 0.08, | 2.16) | 0.42 ( 0.08, | 2.18) | -0.01 (-0.02, 0.01) | |
| >=65 | 1670 | 37 | 2.2 | 1739 | 22 | 1.3 | 0.0334 | 0.57 ( 0.34, | 0.96) | 0.57 ( 0.33, | 0.96) | -0.01 (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | 0.5557 |
| North America | 273 | 9 | 3.3 | 273 | 5 | 1.8 | 0.2788 | 0.56 ( 0.19, | 1.64) | 0.55 ( 0.18, | 1.65) | -0.01 (-0.04, 0.01) | |
| Latin America | 511 | 8 | 1.6 | 504 | 3 | 0.6 | 0.1355 | 0.38 ( 0.10, | 1.42) | 0.38 ( 0.10, | 1.43) | -0.01 (-0.02, 0.00) | |
| Europe | 865 | 13 | 1.5 | 894 | 5 | 0.6 | 0.0493 | 0.37 ( 0.13, | 1.04) | 0.37 ( 0.13, | 1.04) | -0.01 (-0.02, 0.00) | |
| Asia | 231 | 11 | 4.8 | 248 | 8 | 3.2 | 0.3894 | 0.68 ( 0.28, | 1.65) | 0.67 ( 0.26, | 1.69) | -0.02 (-0.05, 0.02) | |
| Other | 121 | 1 | 0.8 | 133 | 3 | 2.3 | 0.3608 | 2.73 ( 0.29, | 25.89) | 2.77 ( 0.28, | 26.99) | 0.01 (-0.02, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.1170 |
| Diabetic | 1045 | 29 | 2.8 | 1081 | 12 | 1.1 | 0.0053 | 0.40 ( 0.21, | 0.78) | 0.39 ( 0.20, | 0.77) | -0.02 (-0.03, 0.00) | |
| Non-Diabetic | 956 | 13 | 1.4 | 971 | 12 | 1.2 | 0.8099 | 0.91 ( 0.42, | 1.98) | 0.91 ( 0.41, | 2.00) | 0.00 (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.6251 |
| <30 | 1086 | 24 | 2.2 | 1094 | 12 | 1.1 | 0.0415 | 0.50 ( 0.25, | 0.99) | 0.49 ( 0.24, | 0.99) | -0.01 (-0.02, 0.00) | |
| >=30 | 915 | 18 | 2.0 | 958 | 12 | 1.3 | 0.2182 | 0.64 ( 0.31, | 1.31) | 0.63 ( 0.30, | 1.32) | -0.01 (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.2332 |
| <130 | 827 | 13 | 1.6 | 853 | 11 | 1.3 | 0.6258 | 0.82 ( 0.37, | 1.82) | 0.82 ( 0.36, | 1.84) | 0.00 (-0.01, 0.01) | |
| >=130 | 1174 | 29 | 2.5 | 1199 | 13 | 1.1 | 0.0105 | 0.44 ( 0.23, | 0.84) | 0.43 ( 0.22, | 0.84) | -0.01 (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.9056 |
| <75 | 935 | 24 | 2.6 | 934 | 13 | 1.4 | 0.0683 | 0.54 ( 0.28, | 1.06) | 0.54 ( 0.27, | 1.06) | -0.01 (-0.02, 0.00) | |
| 75 to <85 | 657 | 11 | 1.7 | 703 | 6 | 0.9 | 0.1734 | 0.51 ( 0.19, | 1.37) | 0.51 ( 0.19, | 1.37) | -0.01 (-0.02, 0.00) | |
| >=85 | 409 | 7 | 1.7 | 415 | 5 | 1.2 | 0.5438 | 0.70 ( 0.23, | 2.20) | 0.70 ( 0.22, | 2.22) | -0.01 (-0.02, 0.01) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Blood and lymphatic system disorders
Preferred term: Iron deficiency anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.8273 |
| <30 | 161 | 7 | 4.3 | 148 | 3 | 2.0 | 0.2495 | 0.47 ( 0.12, | 1.77) | 0.46 ( 0.12, | 1.79) | -0.02 (-0.06, 0.02) | |
| 30 to <45 | 550 | 11 | 2.0 | 564 | 8 | 1.4 | 0.4536 | 0.71 ( 0.29, | 1.75) | 0.71 ( 0.28, | 1.77) | -0.01 (-0.02, 0.01) | |
| >=45 | 1289 | 24 | 1.9 | 1340 | 13 | 1.0 | 0.0523 | 0.52 ( 0.27, | 1.02) | 0.52 ( 0.26, | 1.02) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.7105 |
| Normal (<30) | 764 | 15 | 2.0 | 787 | 8 | 1.0 | 0.1230 | 0.52 ( 0.22, | 1.21) | 0.51 ( 0.22, | 1.22) | -0.01 (-0.02, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 21 | 2.3 | 938 | 14 | 1.5 | 0.2116 | 0.65 ( 0.33, | 1.28) | 0.65 ( 0.33, | 1.28) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 311 | 6 | 1.9 | 318 | 2 | 0.6 | 0.1457 | 0.33 ( 0.07, | 1.60) | 0.32 ( 0.06, | 1.61) | -0.01 (-0.03, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.2049 |
| Low, moderate or high | 1477 | 30 | 2.0 | 1548 | 14 | 0.9 | 0.0097 | 0.45 ( 0.24, | 0.84) | 0.44 ( 0.23, | 0.83) | -0.01 (-0.02, 0.00) | |
| Very high | 519 | 12 | 2.3 | 495 | 10 | 2.0 | 0.7498 | 0.87 ( 0.38, | 2.00) | 0.87 ( 0.37, | 2.03) | 0.00 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.6326 |
| No | 411 | 7 | 1.7 | 410 | 5 | 1.2 | 0.5637 | 0.72 ( 0.23, | 2.24) | 0.71 ( 0.22, | 2.26) | 0.00 (-0.02, 0.01) | |
| Yes | 1590 | 35 | 2.2 | 1642 | 19 | 1.2 | 0.0206 | 0.53 ( 0.30, | 0.91) | 0.52 ( 0.30, | 0.91) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.2433 |
| No | 282 | 6 | 2.1 | 277 | 1 | 0.4 | 0.0604 | 0.17 ( 0.02, | 1.40) | 0.17 ( 0.02, | 1.39) | -0.02 (-0.04, 0.00) | |
| Yes | 1719 | 36 | 2.1 | 1775 | 23 | 1.3 | 0.0671 | 0.62 ( 0.37, | 1.04) | 0.61 ( 0.36, | 1.04) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.2833 |
| No | 229 | 5 | 2.2 | 250 | 1 | 0.4 | 0.0796 | 0.18 ( 0.02, | 1.56) | 0.18 ( 0.02, | 1.55) | -0.02 (-0.04, 0.00) | |
| Yes | 1772 | 37 | 2.1 | 1802 | 23 | 1.3 | 0.0590 | 0.61 ( 0.36, | 1.02) | 0.61 ( 0.36, | 1.02) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Thrombocytopenia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 26 | 1.3 | 2052 | 21 | 1.0 | 0.4120 | 0.79 ( 0.44, 1.40) | 0.79 ( 0.44, 1.40) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Glomerular filtration rate decreased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 27 | 1.3 | 2052 | 23 | 1.1 | 0.5100 | 0.83 ( 0.48, 1.44) | 0.83 ( 0.47, 1.45) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Weight decreased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 25 | 1.2 | 2052 | 27 | 1.3 | 0.8510 | 1.05 ( 0.61, 1.81) | 1.05 ( 0.61, 1.82) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Gamma-glutamyltransferase increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 21 | 1.0 | 2052 | 12 | 0.6 | 0.0998 | 0.56 ( 0.27, 1.13) | 0.55 ( 0.27, 1.13) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Pruritus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 36 | 1.8 | 2052 | 47 | 2.3 | 0.2695 | 1.27 ( 0.83, 1.96) | 1.28 ( 0.83, 1.98) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Skin ulcer

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 35 | 1.7 | 2052 | 27 | 1.3 | 0.2611 | 0.75 ( 0.46, 1.24) | 0.75 ( 0.45, 1.24) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Insomnia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 47 | 2.3 | 2052 | 53 | 2.6 | 0.6311 | 1.10 ( 0.75, 1.62) | 1.10 ( 0.74, 1.64) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Depression

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 34 | 1.7 | 2052 | 44 | 2.1 | 0.3024 | 1.26 ( 0.81, 1.97) | 1.27 ( 0.81, 1.99) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Anxiety

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 39 | 1.9 | 2052 | 29 | 1.4 | 0.1843 | 0.73 ( 0.45, 1.17) | 0.72 ( 0.44, 1.17) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Preferred term: Basal cell carcinoma

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 24 | 1.2 | 2052 | 14 | 0.7 | 0.0876 | 0.57 ( 0.30, | 1.10) | 0.57 ( 0.29, | 1.10) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders
Preferred term: Cataract

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 46 | 2.3 | 2052 | 64 | 3.1 | 0.1082 | 1.36 ( 0.93, 1.97) | 1.37 ( 0.93, 2.01) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders
Preferred term: Cholelithiasis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 31 | 1.5 | 2052 | 19 | 0.9 | 0.0723 | 0.60 ( 0.34, 1.05) | 0.59 ( 0.33, 1.05) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Reproductive system and breast disorders
Preferred term: Benign prostatic hyperplasia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 33 | 1.6 | 2052 | 37 | 1.8 | 0.7068 | 1.09 ( 0.69, 1.74) | 1.10 ( 0.68, 1.76) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Ear and labyrinth disorders
Preferred term: Vertigo

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 35 | 1.7 | 2052 | 34 | 1.7 | 0.8205 | 0.95 ( 0.59, 1.51) | 0.95 ( 0.59, 1.52) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Endocrine disorders
Preferred term: Hypothyroidism

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 33 | 1.6 | 2052 | 31 | 1.5 | 0.7237 | 0.92 ( 0.56, 1.49) | 0.91 ( 0.56, 1.50) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 516 | 25.8 | 2052 | 417 | 20.3 | <0.0001 | 0.79 ( 0.70, 0.88) | 0.73 ( 0.63, 0.85) | -0.05 (-0.08,-0.03) | |
| Sex | | | | | | | | | | | 0.3917 |
| Male | 1065 | 286 | 26.9 | 1093 | 221 | 20.2 | 0.0003 | 0.75 ( 0.65, 0.88) | 0.69 ( 0.56, 0.84) | -0.07 (-0.10,-0.03) | |
| Female | 936 | 230 | 24.6 | 959 | 196 | 20.4 | 0.0311 | 0.83 ( 0.70, 0.98) | 0.79 ( 0.64, 0.98) | -0.04 (-0.08, 0.00) | |
| Age [years] | | | | | | | | | | | 0.0306 |
| <65 | 331 | 71 | 21.5 | 313 | 71 | 22.7 | 0.7059 | 1.06 ( 0.79, 1.41) | 1.07 ( 0.74, 1.56) | 0.01 (-0.05, 0.08) | |
| >=65 | 1670 | 445 | 26.6 | 1739 | 346 | 19.9 | <0.0001 | 0.75 ( 0.66, 0.84) | 0.68 ( 0.58, 0.80) | -0.07 (-0.10,-0.04) | |
| Region | | | | | | | | | | | 0.7706 |
| North America | 273 | 55 | 20.1 | 273 | 48 | 17.6 | 0.4438 | 0.87 ( 0.62, 1.24) | 0.85 ( 0.55, 1.30) | -0.03 (-0.09, 0.04) | |
| Latin America | 511 | 135 | 26.4 | 504 | 114 | 22.6 | 0.1595 | 0.86 ( 0.69, 1.06) | 0.81 ( 0.61, 1.08) | -0.04 (-0.09, 0.01) | |
| Europe | 865 | 237 | 27.4 | 894 | 178 | 19.9 | 0.0002 | 0.73 ( 0.61, 0.86) | 0.66 ( 0.53, 0.82) | -0.07 (-0.11,-0.04) | |
| Asia | 231 | 56 | 24.2 | 248 | 47 | 19.0 | 0.1590 | 0.78 ( 0.55, 1.10) | 0.73 ( 0.47, 1.13) | -0.05 (-0.13, 0.02) | |
| Other | 121 | 33 | 27.3 | 133 | 30 | 22.6 | 0.3847 | 0.83 ( 0.54, 1.27) | 0.78 ( 0.44, 1.37) | -0.05 (-0.15, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.7118 |
| Diabetic | 1045 | 289 | 27.7 | 1081 | 231 | 21.4 | 0.0007 | 0.77 ( 0.66, 0.90) | 0.71 ( 0.58, 0.87) | -0.06 (-0.10,-0.03) | |
| Non-Diabetic | 956 | 227 | 23.7 | 971 | 186 | 19.2 | 0.0141 | 0.81 ( 0.68, 0.96) | 0.76 ( 0.61, 0.95) | -0.05 (-0.08,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.5089 |
| <30 | 1086 | 287 | 26.4 | 1094 | 220 | 20.1 | 0.0005 | 0.76 ( 0.65, 0.89) | 0.70 ( 0.57, 0.86) | -0.06 (-0.10,-0.03) | |
| >=30 | 915 | 229 | 25.0 | 958 | 197 | 20.6 | 0.0212 | 0.82 ( 0.69, 0.97) | 0.78 ( 0.62, 0.96) | -0.04 (-0.08,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.8198 |
| <130 | 827 | 228 | 27.6 | 853 | 188 | 22.0 | 0.0087 | 0.80 ( 0.68, 0.95) | 0.74 ( 0.59, 0.93) | -0.06 (-0.10,-0.01) | |
| >=130 | 1174 | 288 | 24.5 | 1199 | 229 | 19.1 | 0.0014 | 0.78 ( 0.67, 0.91) | 0.73 ( 0.60, 0.88) | -0.05 (-0.09,-0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.1092 |
| <75 | 935 | 244 | 26.1 | 934 | 217 | 23.2 | 0.1511 | 0.89 ( 0.76, 1.04) | 0.86 ( 0.69, 1.06) | -0.03 (-0.07, 0.01) | |
| 75 to <85 | 657 | 171 | 26.0 | 703 | 125 | 17.8 | 0.0002 | 0.68 ( 0.56, 0.84) | 0.61 ( 0.47, 0.80) | -0.08 (-0.13,-0.04) | |
| >=85 | 409 | 101 | 24.7 | 415 | 75 | 18.1 | 0.0204 | 0.73 ( 0.56, 0.95) | 0.67 ( 0.48, 0.94) | -0.07 (-0.12,-0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3633 |
| <30 | 161 | 51 | 31.7 | 148 | 44 | 29.7 | 0.7109 | 0.94 ( 0.67, 1.31) | 0.91 ( 0.56, 1.48) | -0.02 (-0.12, 0.08) | |
| 30 to <45 | 550 | 153 | 27.8 | 564 | 132 | 23.4 | 0.0914 | 0.84 ( 0.69, 1.03) | 0.79 ( 0.61, 1.04) | -0.04 (-0.10, 0.01) | |
| >=45 | 1289 | 312 | 24.2 | 1340 | 241 | 18.0 | <0.0001 | 0.74 ( 0.64, 0.86) | 0.69 ( 0.57, 0.83) | -0.06 (-0.09,-0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.4904 |
| Normal (<30) | 764 | 179 | 23.4 | 787 | 134 | 17.0 | 0.0017 | 0.73 ( 0.59, 0.89) | 0.67 ( 0.52, 0.86) | -0.06 (-0.10,-0.02) | |
| Microalbuminuria (30 to <=300) | 921 | 245 | 26.6 | 938 | 201 | 21.4 | 0.0090 | 0.81 ( 0.68, 0.95) | 0.75 ( 0.61, 0.93) | -0.05 (-0.09,-0.01) | |
| Macroalbuminuria (>300) | 311 | 91 | 29.3 | 318 | 82 | 25.8 | 0.3293 | 0.88 ( 0.68, 1.14) | 0.84 ( 0.59, 1.19) | -0.03 (-0.10, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.1129 |
| Low, moderate or high | 1477 | 358 | 24.2 | 1548 | 281 | 18.2 | <0.0001 | 0.75 ( 0.65, 0.86) | 0.69 ( 0.58, 0.83) | -0.06 (-0.09,-0.03) | |
| Very high | 519 | 157 | 30.3 | 495 | 136 | 27.5 | 0.3297 | 0.91 ( 0.75, 1.10) | 0.87 ( 0.67, 1.15) | -0.03 (-0.08, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.1237 |
| No | 411 | 114 | 27.7 | 410 | 105 | 25.6 | 0.4907 | 0.92 ( 0.74, 1.16) | 0.90 ( 0.66, 1.22) | -0.02 (-0.08, 0.04) | |
| Yes | 1590 | 402 | 25.3 | 1642 | 312 | 19.0 | <0.0001 | 0.75 ( 0.66, 0.86) | 0.69 ( 0.59, 0.82) | -0.06 (-0.09,-0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.1429 |
| No | 282 | 72 | 25.5 | 277 | 68 | 24.5 | 0.7885 | 0.96 ( 0.72, 1.28) | 0.95 ( 0.65, 1.39) | -0.01 (-0.08, 0.06) | |
| Yes | 1719 | 444 | 25.8 | 1775 | 349 | 19.7 | <0.0001 | 0.76 ( 0.67, 0.86) | 0.70 ( 0.60, 0.82) | -0.06 (-0.09,-0.03) | |
| Baseline use of diuretics | | | | | | | | | | | 0.6998 |
| No | 229 | 39 | 17.0 | 250 | 31 | 12.4 | 0.1518 | 0.73 ( 0.47, 1.13) | 0.69 ( 0.41, 1.15) | -0.05 (-0.11, 0.02) | |
| Yes | 1772 | 477 | 26.9 | 1802 | 386 | 21.4 | 0.0001 | 0.80 ( 0.71, 0.89) | 0.74 ( 0.63, 0.86) | -0.05 (-0.08,-0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 59 | 2.9 | 2052 | 74 | 3.6 | 0.2400 | 1.22 ( 0.87, 1.71) | 1.23 ( 0.87, 1.74) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 72 | 3.6 | 2052 | 56 | 2.7 | 0.1137 | 0.76 ( 0.54, 1.07) | 0.75 ( 0.53, 1.07) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 47 | 2.3 | 2052 | 50 | 2.4 | 0.8549 | 1.04 ( 0.70, 1.54) | 1.04 ( 0.69, 1.55) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 21 | 1.0 | 2052 | 33 | 1.6 | 0.1209 | 1.53 ( 0.89, 2.64) | 1.54 ( 0.89, 2.67) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 32 | 1.6 | 2052 | 19 | 0.9 | 0.0545 | 0.58 ( 0.33, 1.02) | 0.58 ( 0.32, 1.02) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure chronic

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 26 | 1.3 | 2052 | 31 | 1.5 | 0.5678 | 1.16 ( 0.69, 1.95) | 1.17 ( 0.69, 1.97) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina unstable

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 16 | 0.8 | 2052 | 23 | 1.1 | 0.2949 | 1.40 ( 0.74, 2.65) | 1.41 ( 0.74, 2.67) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Coronary artery disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 22 | 1.1 | 2052 | 16 | 0.8 | 0.2910 | 0.71 ( 0.37, 1.35) | 0.71 ( 0.37, 1.35) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 21 | 1.0 | 2052 | 18 | 0.9 | 0.5743 | 0.84 ( 0.45, | 1.56) | 0.83 ( 0.44, | 1.57) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 115 | 5.7 | 2052 | 111 | 5.4 | 0.6394 | 0.94 ( 0.73, 1.21) | 0.94 ( 0.72, 1.23) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: COVID-19

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 45 | 2.2 | 2052 | 44 | 2.1 | 0.8202 | 0.95 ( 0.63, 1.44) | 0.95 ( 0.63, 1.45) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 29 | 1.4 | 2052 | 38 | 1.9 | 0.3149 | 1.28 ( 0.79, 2.06) | 1.28 ( 0.79, 2.09) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Sepsis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 24 | 1.2 | 2052 | 33 | 1.6 | 0.2692 | 1.34 ( 0.80, 2.26) | 1.35 ( 0.79, 2.29) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Cellulitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 12 | 0.6 | 2052 | 26 | 1.3 | 0.0275 | 2.11 ( 1.07, 4.18) | 2.13 ( 1.07, 4.23) | 0.01 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | 0.8758 |
| Male | 1065 | 8 | 0.8 | 1093 | 18 | 1.6 | 0.0566 | 2.19 ( 0.96, 5.02) | 2.21 ( 0.96, 5.11) | 0.01 ( 0.00, 0.02) | |
| Female | 936 | 4 | 0.4 | 959 | 8 | 0.8 | 0.2643 | 1.95 ( 0.59, 6.46) | 1.96 ( 0.59, 6.53) | 0.00 ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | 0.7367 |
| <65 | 331 | 2 | 0.6 | 313 | 3 | 1.0 | 0.6087 | 1.59 ( 0.27, 9.43) | 1.59 ( 0.26, 9.59) | 0.00 (-0.01, 0.02) | |
| >=65 | 1670 | 10 | 0.6 | 1739 | 23 | 1.3 | 0.0310 | 2.21 ( 1.05, 4.63) | 2.22 ( 1.06, 4.69) | 0.01 ( 0.00, 0.01) | |
| Region | | | | | | | | | | | 0.4492 |
| North America | 273 | 5 | 1.8 | 273 | 13 | 4.8 | 0.0552 | 2.60 ( 0.94, 7.19) | 2.68 ( 0.94, 7.62) | 0.03 ( 0.00, 0.06) | |
| Latin America | 511 | 1 | 0.2 | 504 | 3 | 0.6 | 0.3097 | 3.04 ( 0.32, 29.14) | 3.05 ( 0.32, 29.46) | 0.00 ( 0.00, 0.01) | |
| Europe | 865 | 1 | 0.1 | 894 | 6 | 0.7 | 0.0643 | 5.81 ( 0.70, 48.12) | 5.84 ( 0.70, 48.59) | 0.01 ( 0.00, 0.01) | |
| Asia | 231 | 1 | 0.4 | 248 | 1 | 0.4 | 0.9599 | 0.93 ( 0.06, 14.81) | 0.93 ( 0.06, 14.97) | 0.00 (-0.01, 0.01) | |
| Other | 121 | 4 | 3.3 | 133 | 3 | 2.3 | 0.6096 | 0.68 ( 0.16, 2.99) | 0.68 ( 0.15, 3.08) | -0.01 (-0.05, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.0249 |
| Diabetic | 1045 | 9 | 0.9 | 1081 | 9 | 0.8 | 0.9425 | 0.97 ( 0.39, 2.43) | 0.97 ( 0.38, 2.44) | 0.00 (-0.01, 0.01) | |
| Non-Diabetic | 956 | 3 | 0.3 | 971 | 17 | 1.8 | 0.0019 | 5.58 ( 1.64, 18.98) | 5.66 ( 1.65, 19.38) | 0.01 ( 0.01, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.1762 |
| <30 | 1086 | 2 | 0.2 | 1094 | 10 | 0.9 | 0.0213 | 4.96 ( 1.09, 22.60) | 5.00 ( 1.09, 22.87) | 0.01 ( 0.00, 0.01) | |
| >=30 | 915 | 10 | 1.1 | 958 | 16 | 1.7 | 0.2858 | 1.53 ( 0.70, 3.35) | 1.54 ( 0.69, 3.41) | 0.01 ( 0.00, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.6669 |
| <130 | 827 | 6 | 0.7 | 853 | 15 | 1.8 | 0.0568 | 2.42 ( 0.94, 6.22) | 2.45 ( 0.95, 6.34) | 0.01 ( 0.00, 0.02) | |
| >=130 | 1174 | 6 | 0.5 | 1199 | 11 | 0.9 | 0.2406 | 1.80 ( 0.67, 4.84) | 1.80 ( 0.66, 4.89) | 0.00 ( 0.00, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.5887 |
| <75 | 935 | 6 | 0.6 | 934 | 16 | 1.7 | 0.0318 | 2.67 ( 1.05, 6.79) | 2.70 ( 1.05, 6.93) | 0.01 ( 0.00, 0.02) | |
| 75 to <85 | 657 | 4 | 0.6 | 703 | 5 | 0.7 | 0.8159 | 1.17 ( 0.32, 4.33) | 1.17 ( 0.31, 4.37) | 0.00 (-0.01, 0.01) | |
| >=85 | 409 | 2 | 0.5 | 415 | 5 | 1.2 | 0.2630 | 2.46 ( 0.48, 12.63) | 2.48 ( 0.48, 12.86) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Cellulitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.6513 |
| <30 | 161 | 1 | 0.6 | 148 | 2 | 1.4 | 0.5131 | 2.18 ( 0.20, 23.75) | 2.19 ( 0.20, 24.43) | 0.01 (-0.01, 0.03) | |
| 30 to <45 | 550 | 6 | 1.1 | 564 | 9 | 1.6 | 0.4648 | 1.46 ( 0.52, 4.08) | 1.47 ( 0.52, 4.16) | 0.01 (-0.01, 0.02) | |
| >=45 | 1289 | 5 | 0.4 | 1340 | 15 | 1.1 | 0.0309 | 2.89 ( 1.05, 7.92) | 2.91 ( 1.05, 8.02) | 0.01 ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.2876 |
| Normal (<30) | 764 | 2 | 0.3 | 787 | 7 | 0.9 | 0.1037 | 3.40 ( 0.71, 16.30) | 3.42 ( 0.71, 16.51) | 0.01 ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 6 | 0.7 | 938 | 16 | 1.7 | 0.0356 | 2.62 ( 1.03, 6.66) | 2.65 ( 1.03, 6.79) | 0.01 ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 311 | 4 | 1.3 | 318 | 3 | 0.9 | 0.6820 | 0.73 ( 0.17, 3.25) | 0.73 ( 0.16, 3.29) | 0.00 (-0.02, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.3150 |
| Low, moderate or high | 1477 | 6 | 0.4 | 1548 | 18 | 1.2 | 0.0191 | 2.86 ( 1.14, 7.19) | 2.88 ( 1.14, 7.29) | 0.01 ( 0.00, 0.01) | |
| Very high | 519 | 6 | 1.2 | 495 | 8 | 1.6 | 0.5303 | 1.40 ( 0.49, 4.00) | 1.40 ( 0.48, 4.08) | 0.00 (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.9303 |
| No | 411 | 3 | 0.7 | 410 | 6 | 1.5 | 0.3129 | 2.00 ( 0.50, 7.96) | 2.02 ( 0.50, 8.13) | 0.01 (-0.01, 0.02) | |
| Yes | 1590 | 9 | 0.6 | 1642 | 20 | 1.2 | 0.0494 | 2.15 ( 0.98, 4.71) | 2.17 ( 0.98, 4.77) | 0.01 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6125 |
| No | 282 | 2 | 0.7 | 277 | 6 | 2.2 | 0.1471 | 3.05 ( 0.62, 15.00) | 3.10 ( 0.62, 15.49) | 0.01 (-0.01, 0.03) | |
| Yes | 1719 | 10 | 0.6 | 1775 | 20 | 1.1 | 0.0809 | 1.94 ( 0.91, 4.13) | 1.95 ( 0.91, 4.17) | 0.01 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.8600 |
| No | 229 | 0 | 0 | 250 | 1 | 0.4 | 0.5174 | 2.75 ( 0.11, 67.14) | 2.76 ( 0.11, 68.08) | 0.00 (-0.01, 0.02) | |
| Yes | 1772 | 12 | 0.7 | 1802 | 25 | 1.4 | 0.0360 | 2.05 ( 1.03, 4.06) | 2.06 ( 1.03, 4.12) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: COVID-19 pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 19 | 0.9 | 2052 | 22 | 1.1 | 0.6966 | 1.13 ( 0.61, 2.08) | 1.13 ( 0.61, 2.10) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 117 | 5.8 | 2052 | 90 | 4.4 | 0.0346 | 0.75 ( 0.57, | 0.98) | 0.74 ( 0.56, | 0.98) | -0.01 (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | 0.4120 |
| Male | 1065 | 65 | 6.1 | 1093 | 45 | 4.1 | 0.0360 | 0.67 ( 0.47, | 0.98) | 0.66 ( 0.45, | 0.98) | -0.02 (-0.04, 0.00) | |
| Female | 936 | 52 | 5.6 | 959 | 45 | 4.7 | 0.3940 | 0.84 ( 0.57, | 1.25) | 0.84 ( 0.56, | 1.26) | -0.01 (-0.03, 0.01) | |
| Age [years] | | | | | | | | | | | | | 0.4388 |
| <65 | 331 | 14 | 4.2 | 313 | 13 | 4.2 | 0.9615 | 0.98 ( 0.47, | 2.06) | 0.98 ( 0.45, | 2.12) | 0.00 (-0.03, 0.03) | |
| >=65 | 1670 | 103 | 6.2 | 1739 | 77 | 4.4 | 0.0232 | 0.72 ( 0.54, | 0.96) | 0.70 ( 0.52, | 0.95) | -0.02 (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | 0.6311 |
| North America | 273 | 44 | 16.1 | 273 | 38 | 13.9 | 0.4723 | 0.86 ( 0.58, | 1.29) | 0.84 ( 0.53, | 1.35) | -0.02 (-0.08, 0.04) | |
| Latin America | 511 | 24 | 4.7 | 504 | 20 | 4.0 | 0.5688 | 0.84 ( 0.47, | 1.51) | 0.84 ( 0.46, | 1.54) | -0.01 (-0.03, 0.02) | |
| Europe | 865 | 30 | 3.5 | 894 | 18 | 2.0 | 0.0612 | 0.58 ( 0.33, | 1.03) | 0.57 ( 0.32, | 1.03) | -0.01 (-0.03, 0.00) | |
| Asia | 231 | 9 | 3.9 | 248 | 4 | 1.6 | 0.1244 | 0.41 ( 0.13, | 1.33) | 0.40 ( 0.12, | 1.33) | -0.02 (-0.05, 0.01) | |
| Other | 121 | 10 | 8.3 | 133 | 10 | 7.5 | 0.8256 | 0.91 ( 0.39, | 2.11) | 0.90 ( 0.36, | 2.25) | -0.01 (-0.07, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.4363 |
| Diabetic | 1045 | 77 | 7.4 | 1081 | 55 | 5.1 | 0.0294 | 0.69 ( 0.49, | 0.97) | 0.67 ( 0.47, | 0.96) | -0.02 (-0.04, 0.00) | |
| Non-Diabetic | 956 | 40 | 4.2 | 971 | 35 | 3.6 | 0.5107 | 0.86 ( 0.55, | 1.34) | 0.86 ( 0.54, | 1.36) | -0.01 (-0.02, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.1113 |
| <30 | 1086 | 58 | 5.3 | 1094 | 34 | 3.1 | 0.0095 | 0.58 ( 0.38, | 0.88) | 0.57 ( 0.37, | 0.88) | -0.02 (-0.04,-0.01) | |
| >=30 | 915 | 59 | 6.4 | 958 | 56 | 5.8 | 0.5871 | 0.91 ( 0.64, | 1.29) | 0.90 ( 0.62, | 1.31) | -0.01 (-0.03, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.3103 |
| <130 | 827 | 54 | 6.5 | 853 | 48 | 5.6 | 0.4387 | 0.86 ( 0.59, | 1.26) | 0.85 ( 0.57, | 1.27) | -0.01 (-0.03, 0.01) | |
| >=130 | 1174 | 63 | 5.4 | 1199 | 42 | 3.5 | 0.0273 | 0.65 ( 0.45, | 0.96) | 0.64 ( 0.43, | 0.95) | -0.02 (-0.04, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.4071 |
| <75 | 935 | 67 | 7.2 | 934 | 56 | 6.0 | 0.3077 | 0.84 ( 0.59, | 1.18) | 0.83 ( 0.57, | 1.19) | -0.01 (-0.03, 0.01) | |
| 75 to <85 | 657 | 31 | 4.7 | 703 | 25 | 3.6 | 0.2811 | 0.75 ( 0.45, | 1.26) | 0.74 ( 0.43, | 1.28) | -0.01 (-0.03, 0.01) | |
| >=85 | 409 | 19 | 4.6 | 415 | 9 | 2.2 | 0.0498 | 0.47 ( 0.21, | 1.02) | 0.46 ( 0.20, | 1.02) | -0.02 (-0.05, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6575 |
| <30 | 161 | 19 | 11.8 | 148 | 17 | 11.5 | 0.9313 | 0.97 ( 0.53, 1.80) | 0.97 ( 0.48, 1.95) | 0.00 | (-0.07, 0.07) | |
| 30 to <45 | 550 | 41 | 7.5 | 564 | 32 | 5.7 | 0.2298 | 0.76 ( 0.49, 1.19) | 0.75 ( 0.46, 1.20) | -0.02 | (-0.05, 0.01) | |
| >=45 | 1289 | 57 | 4.4 | 1340 | 41 | 3.1 | 0.0653 | 0.69 ( 0.47, 1.03) | 0.68 ( 0.45, 1.03) | -0.01 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9779 |
| Normal (<30) | 764 | 36 | 4.7 | 787 | 29 | 3.7 | 0.3128 | 0.78 ( 0.48, 1.26) | 0.77 ( 0.47, 1.27) | -0.01 | (-0.03, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 59 | 6.4 | 938 | 44 | 4.7 | 0.1060 | 0.73 ( 0.50, 1.07) | 0.72 ( 0.48, 1.07) | -0.02 | (-0.04, 0.00) | |
| Macroalbuminuria (>300) | 311 | 22 | 7.1 | 318 | 17 | 5.3 | 0.3689 | 0.76 ( 0.41, 1.40) | 0.74 ( 0.39, 1.43) | -0.02 | (-0.06, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7892 |
| Low, moderate or high | 1477 | 67 | 4.5 | 1548 | 52 | 3.4 | 0.0960 | 0.74 ( 0.52, 1.06) | 0.73 ( 0.51, 1.06) | -0.01 | (-0.03, 0.00) | |
| Very high | 519 | 50 | 9.6 | 495 | 38 | 7.7 | 0.2685 | 0.80 ( 0.53, 1.19) | 0.78 ( 0.50, 1.21) | -0.02 | (-0.05, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7305 |
| No | 411 | 27 | 6.6 | 410 | 22 | 5.4 | 0.4667 | 0.82 ( 0.47, 1.41) | 0.81 ( 0.45, 1.44) | -0.01 | (-0.04, 0.02) | |
| Yes | 1590 | 90 | 5.7 | 1642 | 68 | 4.1 | 0.0453 | 0.73 ( 0.54, 0.99) | 0.72 ( 0.52, 0.99) | -0.02 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.7650 |
| No | 282 | 18 | 6.4 | 277 | 12 | 4.3 | 0.2820 | 0.68 ( 0.33, 1.38) | 0.66 ( 0.31, 1.41) | -0.02 | (-0.06, 0.02) | |
| Yes | 1719 | 99 | 5.8 | 1775 | 78 | 4.4 | 0.0659 | 0.76 ( 0.57, 1.02) | 0.75 ( 0.55, 1.02) | -0.01 | (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2457 |
| No | 229 | 11 | 4.8 | 250 | 5 | 2.0 | 0.0881 | 0.42 ( 0.15, 1.18) | 0.40 ( 0.14, 1.18) | -0.03 | (-0.06, 0.00) | |
| Yes | 1772 | 106 | 6.0 | 1802 | 85 | 4.7 | 0.0927 | 0.79 ( 0.60, 1.04) | 0.78 ( 0.58, 1.04) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal impairment

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 42 | 2.1 | 2052 | 51 | 2.5 | 0.4114 | 1.18 ( 0.79, 1.77) | 1.19 ( 0.79, 1.80) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Chronic kidney disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 30 | 1.5 | 2052 | 19 | 0.9 | 0.0950 | 0.62 ( 0.35, 1.09) | 0.61 ( 0.34, 1.09) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 26 | 1.3 | 2052 | 9 | 0.4 | 0.0031 | 0.34 ( 0.16, 0.72) | 0.33 ( 0.16, 0.72) | -0.01 (-0.01, 0.00) | |
| Sex | | | | | | | | | | | 0.7500 |
| Male | 1065 | 16 | 1.5 | 1093 | 5 | 0.5 | 0.0134 | 0.30 ( 0.11, 0.83) | 0.30 ( 0.11, 0.83) | -0.01 (-0.02, 0.00) | |
| Female | 936 | 10 | 1.1 | 959 | 4 | 0.4 | 0.0979 | 0.39 ( 0.12, 1.24) | 0.39 ( 0.12, 1.24) | -0.01 (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | 0.8625 |
| <65 | 331 | 7 | 2.1 | 313 | 2 | 0.6 | 0.1108 | 0.30 ( 0.06, 1.44) | 0.30 ( 0.06, 1.44) | -0.01 (-0.03, 0.00) | |
| >=65 | 1670 | 19 | 1.1 | 1739 | 7 | 0.4 | 0.0136 | 0.35 ( 0.15, 0.84) | 0.35 ( 0.15, 0.84) | -0.01 (-0.01, 0.00) | |
| Region | | | | | | | | | | | 0.7180 |
| North America | 273 | 5 | 1.8 | 273 | 2 | 0.7 | 0.2538 | 0.40 ( 0.08, 2.04) | 0.40 ( 0.08, 2.06) | -0.01 (-0.03, 0.01) | |
| Latin America | 511 | 9 | 1.8 | 504 | 2 | 0.4 | 0.0358 | 0.23 ( 0.05, 1.04) | 0.22 ( 0.05, 1.03) | -0.01 (-0.03, 0.00) | |
| Europe | 865 | 10 | 1.2 | 894 | 3 | 0.3 | 0.0446 | 0.29 ( 0.08, 1.05) | 0.29 ( 0.08, 1.05) | -0.01 (-0.02, 0.00) | |
| Asia | 231 | 0 | 0 | 248 | 1 | 0.4 | 0.5100 | 2.80 ( 0.11, 68.27) | 2.81 ( 0.11, 69.23) | 0.00 (-0.01, 0.02) | |
| Other | 121 | 2 | 1.7 | 133 | 1 | 0.8 | 0.5068 | 0.45 ( 0.04, 4.95) | 0.45 ( 0.04, 5.03) | -0.01 (-0.04, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.4025 |
| Diabetic | 1045 | 13 | 1.2 | 1081 | 6 | 0.6 | 0.0915 | 0.45 ( 0.17, 1.17) | 0.44 ( 0.17, 1.17) | -0.01 (-0.01, 0.00) | |
| Non-Diabetic | 956 | 13 | 1.4 | 971 | 3 | 0.3 | 0.0110 | 0.23 ( 0.06, 0.79) | 0.22 ( 0.06, 0.79) | -0.01 (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.9687 |
| <30 | 1086 | 12 | 1.1 | 1094 | 4 | 0.4 | 0.0432 | 0.33 ( 0.11, 1.02) | 0.33 ( 0.11, 1.02) | -0.01 (-0.01, 0.00) | |
| >=30 | 915 | 14 | 1.5 | 958 | 5 | 0.5 | 0.0295 | 0.34 ( 0.12, 0.94) | 0.34 ( 0.12, 0.94) | -0.01 (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.9345 |
| <130 | 827 | 9 | 1.1 | 853 | 3 | 0.4 | 0.0731 | 0.32 ( 0.09, 1.19) | 0.32 ( 0.09, 1.19) | -0.01 (-0.02, 0.00) | |
| >=130 | 1174 | 17 | 1.4 | 1199 | 6 | 0.5 | 0.0185 | 0.35 ( 0.14, 0.87) | 0.34 ( 0.13, 0.87) | -0.01 (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.2137 |
| <75 | 935 | 12 | 1.3 | 934 | 3 | 0.3 | 0.0197 | 0.25 ( 0.07, 0.88) | 0.25 ( 0.07, 0.88) | -0.01 (-0.02, 0.00) | |
| 75 to <85 | 657 | 10 | 1.5 | 703 | 2 | 0.3 | 0.0147 | 0.19 ( 0.04, 0.85) | 0.18 ( 0.04, 0.85) | -0.01 (-0.02, 0.00) | |
| >=85 | 409 | 4 | 1.0 | 415 | 4 | 1.0 | 0.9835 | 0.99 ( 0.25, 3.91) | 0.99 ( 0.24, 3.97) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.7629 |
| <30 | 161 | 9 | 5.6 | 148 | 2 | 1.4 | 0.0446 | 0.24 ( 0.05, | 1.10) | 0.23 ( 0.05, | 1.09) | -0.04 (-0.08, 0.00) | |
| 30 to <45 | 550 | 8 | 1.5 | 564 | 4 | 0.7 | 0.2283 | 0.49 ( 0.15, | 1.61) | 0.48 ( 0.14, | 1.62) | -0.01 (-0.02, 0.00) | |
| >=45 | 1289 | 9 | 0.7 | 1340 | 3 | 0.2 | 0.0713 | 0.32 ( 0.09, | 1.18) | 0.32 ( 0.09, | 1.18) | 0.00 (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.7702 |
| Normal (<30) | 764 | 6 | 0.8 | 787 | 3 | 0.4 | 0.2948 | 0.49 ( 0.12, | 1.93) | 0.48 ( 0.12, | 1.94) | 0.00 (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 921 | 12 | 1.3 | 938 | 3 | 0.3 | 0.0178 | 0.25 ( 0.07, | 0.87) | 0.24 ( 0.07, | 0.86) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 311 | 8 | 2.6 | 318 | 3 | 0.9 | 0.1192 | 0.37 ( 0.10, | 1.37) | 0.36 ( 0.09, | 1.37) | -0.02 (-0.04, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.7147 |
| Low, moderate or high | 1477 | 12 | 0.8 | 1548 | 5 | 0.3 | 0.0718 | 0.40 ( 0.14, | 1.13) | 0.40 ( 0.14, | 1.13) | 0.00 (-0.01, 0.00) | |
| Very high | 519 | 14 | 2.7 | 495 | 4 | 0.8 | 0.0228 | 0.30 ( 0.10, | 0.90) | 0.29 ( 0.10, | 0.90) | -0.02 (-0.03, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.6019 |
| No | 411 | 5 | 1.2 | 410 | 1 | 0.2 | 0.1018 | 0.20 ( 0.02, | 1.71) | 0.20 ( 0.02, | 1.71) | -0.01 (-0.02, 0.00) | |
| Yes | 1590 | 21 | 1.3 | 1642 | 8 | 0.5 | 0.0120 | 0.37 ( 0.16, | 0.83) | 0.37 ( 0.16, | 0.83) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.8047 |
| No | 282 | 5 | 1.8 | 277 | 2 | 0.7 | 0.2639 | 0.41 ( 0.08, | 2.08) | 0.40 ( 0.08, | 2.09) | -0.01 (-0.03, 0.01) | |
| Yes | 1719 | 21 | 1.2 | 1775 | 7 | 0.4 | 0.0061 | 0.32 ( 0.14, | 0.76) | 0.32 ( 0.14, | 0.76) | -0.01 (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.7950 |
| No | 229 | 2 | 0.9 | 250 | 1 | 0.4 | 0.5118 | 0.46 ( 0.04, | 5.02) | 0.46 ( 0.04, | 5.06) | 0.00 (-0.02, 0.01) | |
| Yes | 1772 | 24 | 1.4 | 1802 | 8 | 0.4 | 0.0039 | 0.33 ( 0.15, | 0.73) | 0.32 ( 0.15, | 0.72) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 38 | 1.9 | 2052 | 33 | 1.6 | 0.4804 | 0.85 ( 0.53, | 1.34) | 0.84 ( 0.53, | 1.35) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Cerebrovascular accident

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 18 | 0.9 | 2052 | 22 | 1.1 | 0.5784 | 1.19 ( 0.64, 2.22) | 1.19 ( 0.64, 2.23) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Chronic obstructive pulmonary disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 33 | 1.6 | 2052 | 26 | 1.3 | 0.3099 | 0.77 ( 0.46, 1.28) | 0.77 ( 0.46, 1.28) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 18 | 0.9 | 2052 | 26 | 1.3 | 0.2590 | 1.41 ( 0.77, 2.56) | 1.41 ( 0.77, 2.59) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypertensive crisis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 25 | 1.2 | 2052 | 16 | 0.8 | 0.1352 | 0.62 ( 0.33, 1.17) | 0.62 ( 0.33, 1.17) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Preferred term: Basal cell carcinoma

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 24 | 1.2 | 2052 | 14 | 0.7 | 0.0876 | 0.57 ( 0.30, | 1.10) | 0.57 ( 0.29, | 1.10) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 55 | 2.7 | 2052 | 69 | 3.4 | 0.2565 | 1.22 ( 0.86, 1.73) | 1.23 ( 0.86, 1.76) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 28 | 1.4 | 2052 | 29 | 1.4 | 0.9699 | 1.01 ( 0.60, 1.69) | 1.01 ( 0.60, 1.70) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 30 | 1.5 | 2052 | 22 | 1.1 | 0.2270 | 0.72 ( 0.41, 1.24) | 0.71 ( 0.41, 1.24) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 216 | 10.8 | 2052 | 149 | 7.3 | <0.0001 | 0.67 ( 0.55, 0.82) | | 0.65 ( 0.52, 0.81) | | -0.04 (-0.05,-0.02) | |
| Sex | | | | | | | | | | | | | 0.6928 |
| Male | 1065 | 113 | 10.6 | 1093 | 81 | 7.4 | 0.0094 | 0.70 ( 0.53, 0.92) | | 0.67 ( 0.50, 0.91) | | -0.03 (-0.06,-0.01) | |
| Female | 936 | 103 | 11.0 | 959 | 68 | 7.1 | 0.0030 | 0.64 ( 0.48, 0.86) | | 0.62 ( 0.45, 0.85) | | -0.04 (-0.06,-0.01) | |
| Age [years] | | | | | | | | | | | | | 0.8271 |
| <65 | 331 | 38 | 11.5 | 313 | 23 | 7.3 | 0.0735 | 0.64 ( 0.39, 1.05) | | 0.61 ( 0.36, 1.05) | | -0.04 (-0.09, 0.00) | |
| >=65 | 1670 | 178 | 10.7 | 1739 | 126 | 7.2 | 0.0005 | 0.68 ( 0.55, 0.85) | | 0.65 ( 0.52, 0.83) | | -0.03 (-0.05,-0.01) | |
| Region | | | | | | | | | | | | | 0.5732 |
| North America | 273 | 19 | 7.0 | 273 | 15 | 5.5 | 0.4787 | 0.79 ( 0.41, 1.52) | | 0.78 ( 0.39, 1.56) | | -0.01 (-0.06, 0.03) | |
| Latin America | 511 | 66 | 12.9 | 504 | 49 | 9.7 | 0.1085 | 0.75 ( 0.53, 1.07) | | 0.73 ( 0.49, 1.07) | | -0.03 (-0.07, 0.01) | |
| Europe | 865 | 96 | 11.1 | 894 | 56 | 6.3 | 0.0003 | 0.56 ( 0.41, 0.77) | | 0.54 ( 0.38, 0.75) | | -0.05 (-0.07,-0.02) | |
| Asia | 231 | 22 | 9.5 | 248 | 15 | 6.0 | 0.1546 | 0.64 ( 0.34, 1.19) | | 0.61 ( 0.31, 1.21) | | -0.03 (-0.08, 0.01) | |
| Other | 121 | 13 | 10.7 | 133 | 14 | 10.5 | 0.9552 | 0.98 ( 0.48, 2.00) | | 0.98 ( 0.44, 2.17) | | 0.00 (-0.08, 0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.4264 |
| Diabetic | 1045 | 128 | 12.2 | 1081 | 83 | 7.7 | 0.0004 | 0.63 ( 0.48, 0.82) | | 0.60 ( 0.45, 0.80) | | -0.05 (-0.07,-0.02) | |
| Non-Diabetic | 956 | 88 | 9.2 | 971 | 66 | 6.8 | 0.0513 | 0.74 ( 0.54, >1.00) | | 0.72 ( 0.52, 1.00) | | -0.02 (-0.05, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.3341 |
| <30 | 1086 | 122 | 11.2 | 1094 | 90 | 8.2 | 0.0178 | 0.73 ( 0.57, 0.95) | | 0.71 ( 0.53, 0.94) | | -0.03 (-0.05,-0.01) | |
| >=30 | 915 | 94 | 10.3 | 958 | 59 | 6.2 | 0.0012 | 0.60 ( 0.44, 0.82) | | 0.57 ( 0.41, 0.80) | | -0.04 (-0.07,-0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.8261 |
| <130 | 827 | 99 | 12.0 | 853 | 67 | 7.9 | 0.0047 | 0.66 ( 0.49, 0.88) | | 0.63 ( 0.45, 0.87) | | -0.04 (-0.07,-0.01) | |
| >=130 | 1174 | 117 | 10.0 | 1199 | 82 | 6.8 | 0.0060 | 0.69 ( 0.52, 0.90) | | 0.66 ( 0.49, 0.89) | | -0.03 (-0.05,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.2777 |
| <75 | 935 | 116 | 12.4 | 934 | 67 | 7.2 | 0.0001 | 0.58 ( 0.43, 0.77) | | 0.55 ( 0.40, 0.75) | | -0.05 (-0.08,-0.03) | |
| 75 to <85 | 657 | 64 | 9.7 | 703 | 50 | 7.1 | 0.0804 | 0.73 ( 0.51, 1.04) | | 0.71 ( 0.48, 1.04) | | -0.03 (-0.06, 0.00) | |
| >=85 | 409 | 36 | 8.8 | 415 | 32 | 7.7 | 0.5693 | 0.88 ( 0.56, 1.38) | | 0.87 ( 0.53, 1.42) | | -0.01 (-0.05, 0.03) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.4217 |
| <30 | 161 | 29 | 18.0 | 148 | 21 | 14.2 | 0.3620 | 0.79 ( 0.47, | 1.32) | 0.75 ( 0.41, | 1.39) | -0.04 (-0.12, 0.04) | |
| 30 to <45 | 550 | 65 | 11.8 | 564 | 52 | 9.2 | 0.1573 | 0.78 ( 0.55, | 1.10) | 0.76 ( 0.52, | 1.11) | -0.03 (-0.06, 0.01) | |
| >=45 | 1289 | 122 | 9.5 | 1340 | 76 | 5.7 | 0.0002 | 0.60 ( 0.45, | 0.79) | 0.58 ( 0.43, | 0.77) | -0.04 (-0.06,-0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.7598 |
| Normal (<30) | 764 | 76 | 9.9 | 787 | 48 | 6.1 | 0.0052 | 0.61 ( 0.43, | 0.87) | 0.59 ( 0.40, | 0.86) | -0.04 (-0.07,-0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 97 | 10.5 | 938 | 68 | 7.2 | 0.0128 | 0.69 ( 0.51, | 0.93) | 0.66 ( 0.48, | 0.92) | -0.03 (-0.06,-0.01) | |
| Macroalbuminuria (>300) | 311 | 43 | 13.8 | 318 | 33 | 10.4 | 0.1845 | 0.75 ( 0.49, | 1.15) | 0.72 ( 0.45, | 1.17) | -0.03 (-0.09, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.4447 |
| Low, moderate or high | 1477 | 141 | 9.5 | 1548 | 95 | 6.1 | 0.0005 | 0.64 ( 0.50, | 0.83) | 0.62 ( 0.47, | 0.81) | -0.03 (-0.05,-0.01) | |
| Very high | 519 | 75 | 14.5 | 495 | 54 | 10.9 | 0.0907 | 0.75 ( 0.54, | 1.05) | 0.72 ( 0.50, | 1.05) | -0.04 (-0.08, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.2762 |
| No | 411 | 45 | 10.9 | 410 | 37 | 9.0 | 0.3578 | 0.82 ( 0.55, | 1.25) | 0.81 ( 0.51, | 1.28) | -0.02 (-0.06, 0.02) | |
| Yes | 1590 | 171 | 10.8 | 1642 | 112 | 6.8 | <0.0001 | 0.63 ( 0.50, | 0.80) | 0.61 ( 0.47, | 0.78) | -0.04 (-0.06,-0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.1068 |
| No | 282 | 24 | 8.5 | 277 | 24 | 8.7 | 0.9483 | 1.02 ( 0.59, | 1.75) | 1.02 ( 0.56, | 1.84) | 0.00 (-0.04, 0.05) | |
| Yes | 1719 | 192 | 11.2 | 1775 | 125 | 7.0 | <0.0001 | 0.63 ( 0.51, | 0.78) | 0.60 ( 0.48, | 0.76) | -0.04 (-0.06,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.1614 |
| No | 229 | 7 | 3.1 | 250 | 10 | 4.0 | 0.5773 | 1.31 ( 0.51, | 3.38) | 1.32 ( 0.49, | 3.53) | 0.01 (-0.02, 0.04) | |
| Yes | 1772 | 209 | 11.8 | 1802 | 139 | 7.7 | <0.0001 | 0.65 ( 0.53, | 0.80) | 0.63 ( 0.50, | 0.78) | -0.04 (-0.06,-0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 32 | 1.6 | 2052 | 29 | 1.4 | 0.6269 | 0.88 ( 0.54, 1.46) | 0.88 ( 0.53, 1.46) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 18 | 0.9 | 2052 | 23 | 1.1 | 0.4815 | 1.25 ( 0.67, 2.30) | 1.25 ( 0.67, 2.32) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 22 | 1.1 | 2052 | 18 | 0.9 | 0.4742 | 0.80 ( 0.43, 1.48) | 0.80 ( 0.43, 1.49) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 17 | 0.8 | 2052 | 22 | 1.1 | 0.4681 | 1.26 ( 0.67, 2.37) | 1.26 ( 0.67, 2.39) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 58 | 2.9 | 2052 | 61 | 3.0 | 0.8888 | 1.03 ( 0.72, 1.46) | 1.03 ( 0.71, 1.48) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: COVID-19

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 29 | 1.4 | 2052 | 26 | 1.3 | 0.6162 | 0.87 ( 0.52, 1.48) | 0.87 ( 0.51, 1.49) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Sepsis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 18 | 0.9 | 2052 | 29 | 1.4 | 0.1267 | 1.57 ( 0.88, 2.82) | 1.58 ( 0.87, 2.85) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 2001 | 53 | 2.6 | 2052 | 35 | 1.7 | 0.0394 | 0.64 ( 0.42, 0.98) | 0.64 ( 0.41, 0.98) | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | 0.6899 |
| Male | 1065 | 28 | 2.6 | 1093 | 17 | 1.6 | 0.0809 | 0.59 ( 0.33, 1.07) | 0.59 ( 0.32, 1.08) | -0.01 (-0.02, 0.00) | |
| Female | 936 | 25 | 2.7 | 959 | 18 | 1.9 | 0.2459 | 0.70 ( 0.39, 1.28) | 0.70 ( 0.38, 1.29) | -0.01 (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | 0.3968 |
| <65 | 331 | 5 | 1.5 | 313 | 5 | 1.6 | 0.9290 | 1.06 ( 0.31, 3.62) | 1.06 ( 0.30, 3.69) | 0.00 (-0.02, 0.02) | |
| >=65 | 1670 | 48 | 2.9 | 1739 | 30 | 1.7 | 0.0249 | 0.60 ( 0.38, 0.94) | 0.59 ( 0.37, 0.94) | -0.01 (-0.02, 0.00) | |
| Region | | | | | | | | | | | 0.5096 |
| North America | 273 | 14 | 5.1 | 273 | 12 | 4.4 | 0.6877 | 0.86 ( 0.40, 1.82) | 0.85 ( 0.39, 1.87) | -0.01 (-0.04, 0.03) | |
| Latin America | 511 | 13 | 2.5 | 504 | 11 | 2.2 | 0.7047 | 0.86 ( 0.39, 1.90) | 0.85 ( 0.38, 1.93) | 0.00 (-0.02, 0.02) | |
| Europe | 865 | 16 | 1.8 | 894 | 5 | 0.6 | 0.0127 | 0.30 ( 0.11, 0.82) | 0.30 ( 0.11, 0.82) | -0.01 (-0.02, 0.00) | |
| Asia | 231 | 5 | 2.2 | 248 | 3 | 1.2 | 0.4152 | 0.56 ( 0.14, 2.31) | 0.55 ( 0.13, 2.34) | -0.01 (-0.03, 0.01) | |
| Other | 121 | 5 | 4.1 | 133 | 4 | 3.0 | 0.6282 | 0.73 ( 0.20, 2.65) | 0.72 ( 0.19, 2.74) | -0.01 (-0.06, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.5984 |
| Diabetic | 1045 | 33 | 3.2 | 1081 | 20 | 1.9 | 0.0532 | 0.59 ( 0.34, 1.01) | 0.58 ( 0.33, 1.01) | -0.01 (-0.03, 0.00) | |
| Non-Diabetic | 956 | 20 | 2.1 | 971 | 15 | 1.5 | 0.3684 | 0.74 ( 0.38, 1.43) | 0.73 ( 0.37, 1.44) | -0.01 (-0.02, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.3802 |
| <30 | 1086 | 22 | 2.0 | 1094 | 11 | 1.0 | 0.0511 | 0.50 ( 0.24, 1.02) | 0.49 ( 0.24, 1.02) | -0.01 (-0.02, 0.00) | |
| >=30 | 915 | 31 | 3.4 | 958 | 24 | 2.5 | 0.2580 | 0.74 ( 0.44, 1.25) | 0.73 ( 0.43, 1.26) | -0.01 (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.8742 |
| <130 | 827 | 25 | 3.0 | 853 | 16 | 1.9 | 0.1276 | 0.62 ( 0.33, 1.15) | 0.61 ( 0.33, 1.16) | -0.01 (-0.03, 0.00) | |
| >=130 | 1174 | 28 | 2.4 | 1199 | 19 | 1.6 | 0.1618 | 0.66 ( 0.37, 1.18) | 0.66 ( 0.37, 1.19) | -0.01 (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.6499 |
| <75 | 935 | 29 | 3.1 | 934 | 20 | 2.1 | 0.1939 | 0.69 ( 0.39, 1.21) | 0.68 ( 0.38, 1.22) | -0.01 (-0.02, 0.00) | |
| 75 to <85 | 657 | 14 | 2.1 | 703 | 11 | 1.6 | 0.4373 | 0.73 ( 0.34, 1.61) | 0.73 ( 0.33, 1.62) | -0.01 (-0.02, 0.01) | |
| >=85 | 409 | 10 | 2.4 | 415 | 4 | 1.0 | 0.1000 | 0.39 ( 0.12, 1.25) | 0.39 ( 0.12, 1.25) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.8728 |
| <30 | 161 | 10 | 6.2 | 148 | 7 | 4.7 | 0.5683 | 0.76 ( 0.30, | 1.95) | 0.75 ( 0.28, | 2.02) | -0.01 (-0.07, 0.04) | |
| 30 to <45 | 550 | 19 | 3.5 | 564 | 11 | 2.0 | 0.1210 | 0.56 ( 0.27, | 1.18) | 0.56 ( 0.26, | 1.18) | -0.02 (-0.03, 0.00) | |
| >=45 | 1289 | 24 | 1.9 | 1340 | 17 | 1.3 | 0.2197 | 0.68 ( 0.37, | 1.26) | 0.68 ( 0.36, | 1.27) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.2041 |
| Normal (<30) | 764 | 16 | 2.1 | 787 | 13 | 1.7 | 0.5202 | 0.79 ( 0.38, | 1.63) | 0.79 ( 0.38, | 1.64) | 0.00 (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 28 | 3.0 | 938 | 12 | 1.3 | 0.0089 | 0.42 ( 0.22, | 0.82) | 0.41 ( 0.21, | 0.82) | -0.02 (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 311 | 9 | 2.9 | 318 | 10 | 3.1 | 0.8542 | 1.09 ( 0.45, | 2.64) | 1.09 ( 0.44, | 2.72) | 0.00 (-0.02, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.7797 |
| Low, moderate or high | 1477 | 29 | 2.0 | 1548 | 21 | 1.4 | 0.1907 | 0.69 ( 0.40, | 1.21) | 0.69 ( 0.39, | 1.21) | -0.01 (-0.02, 0.00) | |
| Very high | 519 | 24 | 4.6 | 495 | 14 | 2.8 | 0.1323 | 0.61 ( 0.32, | 1.17) | 0.60 ( 0.31, | 1.17) | -0.02 (-0.04, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.3393 |
| No | 411 | 14 | 3.4 | 410 | 6 | 1.5 | 0.0710 | 0.43 ( 0.17, | 1.11) | 0.42 ( 0.16, | 1.11) | -0.02 (-0.04, 0.00) | |
| Yes | 1590 | 39 | 2.5 | 1642 | 29 | 1.8 | 0.1739 | 0.72 ( 0.45, | 1.16) | 0.72 ( 0.44, | 1.16) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.8215 |
| No | 282 | 10 | 3.5 | 277 | 7 | 2.5 | 0.4830 | 0.71 ( 0.28, | 1.85) | 0.71 ( 0.26, | 1.88) | -0.01 (-0.04, 0.02) | |
| Yes | 1719 | 43 | 2.5 | 1775 | 28 | 1.6 | 0.0530 | 0.63 ( 0.39, | 1.01) | 0.62 ( 0.39, | 1.01) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.9320 |
| No | 229 | 4 | 1.7 | 250 | 3 | 1.2 | 0.6184 | 0.69 ( 0.16, | 3.04) | 0.68 ( 0.15, | 3.09) | -0.01 (-0.03, 0.02) | |
| Yes | 1772 | 49 | 2.8 | 1802 | 32 | 1.8 | 0.0469 | 0.64 ( 0.41, | <1.00) | 0.64 ( 0.41, | 1.00) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal impairment

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 31 | 1.5 | 2052 | 33 | 1.6 | 0.8803 | 1.04 ( 0.64, 1.69) | 1.04 ( 0.63, 1.70) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 54 | 2.7 | 2052 | 68 | 3.3 | 0.2518 | 1.23 ( 0.86, 1.75) | 1.24 ( 0.86, 1.78) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 24 | 1.2 | 2052 | 22 | 1.1 | 0.7021 | 0.89 ( 0.50, 1.59) | 0.89 ( 0.50, 1.60) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 8 | 0.4 | 2052 | 22 | 1.1 | 0.0125 | 2.68 ( 1.20, 6.01) | 2.70 ( 1.20, 6.08) | 0.01 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | 0.7715 |
| Male | 1065 | 5 | 0.5 | 1093 | 15 | 1.4 | 0.0286 | 2.92 ( 1.07, 8.01) | 2.95 ( 1.07, 8.15) | 0.01 ( 0.00, 0.02) | |
| Female | 936 | 3 | 0.3 | 959 | 7 | 0.7 | 0.2187 | 2.28 ( 0.59, 8.78) | 2.29 ( 0.59, 8.87) | 0.00 ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | 0.3138 |
| <65 | 331 | 2 | 0.6 | 313 | 2 | 0.6 | 0.9553 | 1.06 ( 0.15, 7.46) | 1.06 ( 0.15, 7.56) | 0.00 (-0.01, 0.01) | |
| >=65 | 1670 | 6 | 0.4 | 1739 | 20 | 1.2 | 0.0080 | 3.20 ( 1.29, 7.95) | 3.23 ( 1.29, 8.05) | 0.01 ( 0.00, 0.01) | |
| Region | | | | | | | | | | | 0.8246 |
| North America | 273 | 4 | 1.5 | 273 | 13 | 4.8 | 0.0266 | 3.25 ( 1.07, 9.84) | 3.36 ( 1.08, 10.45) | 0.03 ( 0.00, 0.06) | |
| Latin America | 511 | 2 | 0.4 | 504 | 5 | 1.0 | 0.2476 | 2.53 ( 0.49, 13.00) | 2.55 ( 0.49, 13.21) | 0.01 ( 0.00, 0.02) | |
| Europe | 865 | 2 | 0.2 | 894 | 2 | 0.2 | 0.9737 | 0.97 ( 0.14, 6.85) | 0.97 ( 0.14, 6.88) | 0.00 ( 0.00, 0.00) | |
| Asia | 231 | 0 | 0 | 248 | 0 | 0 | 0.9718 | 0.93 ( 0.02, 46.76) | 0.93 ( 0.02, 47.14) | 0.00 (-0.01, 0.01) | |
| Other | 121 | 0 | 0 | 133 | 2 | 1.5 | 0.2797 | 4.55 ( 0.22, 93.88) | 4.62 ( 0.22, 97.19) | 0.01 (-0.01, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.4166 |
| Diabetic | 1045 | 6 | 0.6 | 1081 | 13 | 1.2 | 0.1238 | 2.09 ( 0.80, 5.49) | 2.11 ( 0.80, 5.57) | 0.01 ( 0.00, 0.01) | |
| Non-Diabetic | 956 | 2 | 0.2 | 971 | 9 | 0.9 | 0.0365 | 4.43 ( 0.96, 20.45) | 4.46 ( 0.96, 20.71) | 0.01 ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.5312 |
| <30 | 1086 | 4 | 0.4 | 1094 | 8 | 0.7 | 0.2521 | 1.99 ( 0.60, 6.57) | 1.99 ( 0.60, 6.64) | 0.00 ( 0.00, 0.01) | |
| >=30 | 915 | 4 | 0.4 | 958 | 14 | 1.5 | 0.0231 | 3.34 ( 1.10, 10.12) | 3.38 ( 1.11, 10.30) | 0.01 ( 0.00, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.8343 |
| <130 | 827 | 4 | 0.5 | 853 | 12 | 1.4 | 0.0515 | 2.91 ( 0.94, 8.98) | 2.94 ( 0.94, 9.14) | 0.01 ( 0.00, 0.02) | |
| >=130 | 1174 | 4 | 0.3 | 1199 | 10 | 0.8 | 0.1167 | 2.45 ( 0.77, 7.78) | 2.46 ( 0.77, 7.87) | 0.00 ( 0.00, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.9154 |
| <75 | 935 | 5 | 0.5 | 934 | 15 | 1.6 | 0.0244 | 3.00 ( 1.10, 8.23) | 3.04 ( 1.10, 8.39) | 0.01 ( 0.00, 0.02) | |
| 75 to <85 | 657 | 1 | 0.2 | 703 | 3 | 0.4 | 0.3502 | 2.80 ( 0.29, 26.89) | 2.81 ( 0.29, 27.10) | 0.00 ( 0.00, 0.01) | |
| >=85 | 409 | 2 | 0.5 | 415 | 4 | 1.0 | 0.4228 | 1.97 ( 0.36, 10.70) | 1.98 ( 0.36, 10.87) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.2934 |
| <30 | 161 | 3 | 1.9 | 148 | 3 | 2.0 | 0.9170 | 1.09 ( 0.22, 5.31) | 1.09 ( 0.22, 5.48) | 0.00 (-0.03, 0.03) | |
| 30 to <45 | 550 | 0 | 0 | 564 | 7 | 1.2 | 0.0144 | 14.63 ( 0.84,255.51) | 14.81 ( 0.84,259.96) | 0.01 ( 0.00, 0.02) | |
| >=45 | 1289 | 5 | 0.4 | 1340 | 12 | 0.9 | 0.1045 | 2.31 ( 0.82, 6.53) | 2.32 ( 0.82, 6.61) | 0.01 ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.5521 |
| Normal (<30) | 764 | 2 | 0.3 | 787 | 7 | 0.9 | 0.1037 | 3.40 ( 0.71, 16.30) | 3.42 ( 0.71, 16.51) | 0.01 ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 3 | 0.3 | 938 | 11 | 1.2 | 0.0347 | 3.60 ( 1.01, 12.86) | 3.63 ( 1.01, 13.06) | 0.01 ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 311 | 3 | 1.0 | 318 | 4 | 1.3 | 0.7260 | 1.30 ( 0.29, 5.78) | 1.31 ( 0.29, 5.89) | 0.00 (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.6162 |
| Low, moderate or high | 1477 | 5 | 0.3 | 1548 | 12 | 0.8 | 0.1083 | 2.29 ( 0.81, 6.48) | 2.30 ( 0.81, 6.54) | 0.00 ( 0.00, 0.01) | |
| Very high | 519 | 3 | 0.6 | 495 | 10 | 2.0 | 0.0413 | 3.49 ( 0.97, 12.62) | 3.55 ( 0.97, 12.96) | 0.01 ( 0.00, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.9248 |
| No | 411 | 2 | 0.5 | 410 | 5 | 1.2 | 0.2535 | 2.51 ( 0.49, 12.84) | 2.52 ( 0.49, 13.09) | 0.01 (-0.01, 0.02) | |
| Yes | 1590 | 6 | 0.4 | 1642 | 17 | 1.0 | 0.0261 | 2.74 ( 1.08, 6.94) | 2.76 ( 1.09, 7.02) | 0.01 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6820 |
| No | 282 | 1 | 0.4 | 277 | 4 | 1.4 | 0.1714 | 4.07 ( 0.46, 36.21) | 4.12 ( 0.46, 37.07) | 0.01 ( 0.00, 0.03) | |
| Yes | 1719 | 7 | 0.4 | 1775 | 18 | 1.0 | 0.0334 | 2.49 ( 1.04, 5.95) | 2.51 ( 1.04, 6.01) | 0.01 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9811 |
| No | 229 | 1 | 0.4 | 250 | 3 | 1.2 | 0.3591 | 2.75 ( 0.29, 26.23) | 2.77 ( 0.29, 26.81) | 0.01 (-0.01, 0.02) | |
| Yes | 1772 | 7 | 0.4 | 1802 | 19 | 1.1 | 0.0204 | 2.67 ( 1.12, 6.33) | 2.69 ( 1.13, 6.41) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 14 | 0.7 | 2052 | 29 | 1.4 | 0.0266 | 2.02 ( 1.07, 3.81) | 2.03 ( 1.07, 3.86) | 0.01 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | 0.4354 |
| Male | 1065 | 9 | 0.8 | 1093 | 15 | 1.4 | 0.2429 | 1.62 ( 0.71, 3.69) | 1.63 ( 0.71, 3.75) | 0.01 ( 0.00, 0.01) | |
| Female | 936 | 5 | 0.5 | 959 | 14 | 1.5 | 0.0432 | 2.73 ( 0.99, 7.56) | 2.76 ( 0.99, 7.69) | 0.01 ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | 0.4982 |
| <65 | 331 | 2 | 0.6 | 313 | 2 | 0.6 | 0.9553 | 1.06 ( 0.15, 7.46) | 1.06 ( 0.15, 7.56) | 0.00 (-0.01, 0.01) | |
| >=65 | 1670 | 12 | 0.7 | 1739 | 27 | 1.6 | 0.0221 | 2.16 ( 1.10, 4.25) | 2.18 ( 1.10, 4.32) | 0.01 ( 0.00, 0.02) | |
| Region | | | | | | | | | | | 0.5603 |
| North America | 273 | 3 | 1.1 | 273 | 8 | 2.9 | 0.1278 | 2.67 ( 0.72, 9.95) | 2.72 ( 0.71, 10.35) | 0.02 (-0.01, 0.04) | |
| Latin America | 511 | 1 | 0.2 | 504 | 6 | 1.2 | 0.0555 | 6.08 ( 0.74, 50.35) | 6.14 ( 0.74, 51.22) | 0.01 ( 0.00, 0.02) | |
| Europe | 865 | 7 | 0.8 | 894 | 9 | 1.0 | 0.6628 | 1.24 ( 0.47, 3.33) | 1.25 ( 0.46, 3.36) | 0.00 (-0.01, 0.01) | |
| Asia | 231 | 2 | 0.9 | 248 | 2 | 0.8 | 0.9431 | 0.93 ( 0.13, 6.56) | 0.93 ( 0.13, 6.66) | 0.00 (-0.02, 0.02) | |
| Other | 121 | 1 | 0.8 | 133 | 4 | 3.0 | 0.2114 | 3.64 ( 0.41, 32.11) | 3.72 ( 0.41, 33.76) | 0.02 (-0.01, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.9376 |
| Diabetic | 1045 | 7 | 0.7 | 1081 | 15 | 1.4 | 0.1021 | 2.07 ( 0.85, 5.06) | 2.09 ( 0.85, 5.14) | 0.01 ( 0.00, 0.02) | |
| Non-Diabetic | 956 | 7 | 0.7 | 971 | 14 | 1.4 | 0.1336 | 1.97 ( 0.80, 4.86) | 1.98 ( 0.80, 4.94) | 0.01 ( 0.00, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.5309 |
| <30 | 1086 | 5 | 0.5 | 1094 | 13 | 1.2 | 0.0604 | 2.58 ( 0.92, 7.21) | 2.60 ( 0.92, 7.32) | 0.01 ( 0.00, 0.01) | |
| >=30 | 915 | 9 | 1.0 | 958 | 16 | 1.7 | 0.1956 | 1.70 ( 0.75, 3.82) | 1.71 ( 0.75, 3.89) | 0.01 ( 0.00, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.7445 |
| <130 | 827 | 6 | 0.7 | 853 | 11 | 1.3 | 0.2481 | 1.78 ( 0.66, 4.78) | 1.79 ( 0.66, 4.86) | 0.01 ( 0.00, 0.02) | |
| >=130 | 1174 | 8 | 0.7 | 1199 | 18 | 1.5 | 0.0551 | 2.20 ( 0.96, 5.05) | 2.22 ( 0.96, 5.13) | 0.01 ( 0.00, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.5162 |
| <75 | 935 | 10 | 1.1 | 934 | 15 | 1.6 | 0.3128 | 1.50 ( 0.68, 3.33) | 1.51 ( 0.67, 3.38) | 0.01 (-0.01, 0.02) | |
| 75 to <85 | 657 | 3 | 0.5 | 703 | 10 | 1.4 | 0.0674 | 3.12 ( 0.86, 11.27) | 3.15 ( 0.86, 11.48) | 0.01 ( 0.00, 0.02) | |
| >=85 | 409 | 1 | 0.2 | 415 | 4 | 1.0 | 0.1837 | 3.94 ( 0.44, 35.12) | 3.97 ( 0.44, 35.68) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3967 |
| <30 | 161 | 1 | 0.6 | 148 | 6 | 4.1 | 0.0428 | 6.53 ( 0.80, 53.58) | 6.76 ( 0.80, 56.83) | 0.03 ( 0.00, 0.07) | |
| 30 to <45 | 550 | 6 | 1.1 | 564 | 8 | 1.4 | 0.6237 | 1.30 ( 0.45, 3.72) | 1.30 ( 0.45, 3.78) | 0.00 (-0.01, 0.02) | |
| >=45 | 1289 | 7 | 0.5 | 1340 | 15 | 1.1 | 0.1049 | 2.06 ( 0.84, 5.04) | 2.07 ( 0.84, 5.10) | 0.01 ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.7617 |
| Normal (<30) | 764 | 6 | 0.8 | 787 | 10 | 1.3 | 0.3443 | 1.62 ( 0.59, 4.43) | 1.63 ( 0.59, 4.50) | 0.00 (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 921 | 7 | 0.8 | 938 | 15 | 1.6 | 0.0944 | 2.10 ( 0.86, 5.14) | 2.12 ( 0.86, 5.23) | 0.01 ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 311 | 1 | 0.3 | 318 | 4 | 1.3 | 0.1861 | 3.91 ( 0.44, 34.80) | 3.95 ( 0.44, 35.53) | 0.01 ( 0.00, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.4598 |
| Low, moderate or high | 1477 | 10 | 0.7 | 1548 | 18 | 1.2 | 0.1632 | 1.72 ( 0.80, 3.71) | 1.73 ( 0.79, 3.75) | 0.00 ( 0.00, 0.01) | |
| Very high | 519 | 4 | 0.8 | 495 | 11 | 2.2 | 0.0556 | 2.88 ( 0.92, 9.00) | 2.93 ( 0.93, 9.25) | 0.01 ( 0.00, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.4058 |
| No | 411 | 5 | 1.2 | 410 | 14 | 3.4 | 0.0362 | 2.81 ( 1.02, 7.72) | 2.87 ( 1.02, 8.04) | 0.02 ( 0.00, 0.04) | |
| Yes | 1590 | 9 | 0.6 | 1642 | 15 | 0.9 | 0.2500 | 1.61 ( 0.71, 3.68) | 1.62 ( 0.71, 3.71) | 0.00 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.4253 |
| No | 282 | 2 | 0.7 | 277 | 7 | 2.5 | 0.0878 | 3.56 ( 0.75, 17.00) | 3.63 ( 0.75, 17.63) | 0.02 ( 0.00, 0.04) | |
| Yes | 1719 | 12 | 0.7 | 1775 | 22 | 1.2 | 0.1032 | 1.78 ( 0.88, 3.58) | 1.79 ( 0.88, 3.62) | 0.01 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.2368 |
| No | 229 | 0 | 0 | 250 | 5 | 2.0 | 0.0514 | 10.08 ( 0.56,181.28) | 10.28 ( 0.57,187.01) | 0.02 ( 0.00, 0.04) | |
| Yes | 1772 | 14 | 0.8 | 1802 | 24 | 1.3 | 0.1143 | 1.69 ( 0.87, 3.25) | 1.70 ( 0.87, 3.29) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.2.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 2001 | 22 | 1.1 | 2052 | 17 | 0.8 | 0.3769 | 0.75 ( 0.40, 1.41) | 0.75 ( 0.40, 1.42) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.2.2.6**

R.2.2.6 Medical concepts for adverse events of special interest and other specific AEs

Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Broad BIcMQ 'Urinary tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)' | Urinary tract malignancy events (BIcMQ) | 40000010 | | 10004986 | Bladder adenocarcinoma recurrent |
| | | | | 10004987 | Bladder adenocarcinoma stage 0 |
| | | | | 10004988 | Bladder adenocarcinoma stage I |
| | | | | 10004989 | Bladder adenocarcinoma stage II |
| | | | | 10004990 | Bladder adenocarcinoma stage III |
| | | | | 10004991 | Bladder adenocarcinoma stage IV |
| | | | | 10004992 | Bladder adenocarcinoma stage unspecified |
| | | | | 10005003 | Bladder cancer |
| | | | | 10005005 | Bladder cancer recurrent |
| | | | | 10005006 | Bladder cancer stage 0, with cancer in situ |
| | | | | 10005007 | Bladder cancer stage 0, without cancer in situ |
| | | | | 10005008 | Bladder cancer stage I, with cancer in situ |
| | | | | 10005009 | Bladder cancer stage I, without cancer in situ |
| | | | | 10005010 | Bladder cancer stage II |
| | | | | 10005011 | Bladder cancer stage III |
| | | | | 10005012 | Bladder cancer stage IV |
| | | | | 10005056 | Bladder neoplasm |
| | | | | 10005075 | Bladder squamous cell carcinoma recurrent |
| | | | | 10005076 | Bladder squamous cell carcinoma stage 0 |
| | | | | 10005077 | Bladder squamous cell carcinoma stage I |
| | | | | 10005078 | Bladder squamous cell carcinoma stage II |
| | | | | 10005079 | Bladder squamous cell carcinoma stage III |
| | | | | 10005080 | Bladder squamous cell carcinoma stage IV |
| | | | | 10005081 | Bladder squamous cell carcinoma stage unspecified |
| | | | | 10005084 | Bladder transitional cell carcinoma |
| | | | | 10009253 | Clear cell sarcoma of the kidney |
| | | | | 10026426 | Malignant neoplasm of renal pelvis |
| | | | | 10027455 | Metastases to kidney |
| | | | | 10029145 | Nephroblastoma |
| | | | | 10033702 | Papillary tumour of renal pelvis |
| | | | | 10038389 | Renal cancer |
| | | | | 10038390 | Renal cancer recurrent |
| | | | | 10038391 | Renal cancer stage I |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Broad BIcMQ 'Urinary tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)' | Urinary tract malignancy events (BIcMQ) | 40000010 | | 10038392 | Renal cancer stage II |
| | | | | 10038393 | Renal cancer stage III |
| | | | | 10038394 | Renal cancer stage IV |
| | | | | 10038410 | Renal cell carcinoma recurrent |
| | | | | 10038411 | Renal cell carcinoma stage I |
| | | | | 10038412 | Renal cell carcinoma stage II |
| | | | | 10038413 | Renal cell carcinoma stage III |
| | | | | 10038414 | Renal cell carcinoma stage IV |
| | | | | 10039019 | Rhabdoid tumour of the kidney |
| | | | | 10044406 | Transitional cell cancer of renal pelvis and ureter metastatic |
| | | | | 10044407 | Transitional cell cancer of the renal pelvis and ureter |
| | | | | 10044408 | Transitional cell cancer of the renal pelvis and ureter localised |
| | | | | 10044410 | Transitional cell cancer of the renal pelvis and ureter recurrent |
| | | | | 10044411 | Transitional cell cancer of the renal pelvis and ureter regional |
| | | | | 10044412 | Transitional cell carcinoma |
| | | | | 10044426 | Transitional cell carcinoma urethra |
| | | | | 10046392 | Ureteric cancer |
| | | | | 10046393 | Ureteric cancer local |
| | | | | 10046394 | Ureteric cancer metastatic |
| | | | | 10046396 | Ureteric cancer recurrent |
| | | | | 10046397 | Ureteric cancer regional |
| | | | | 10046431 | Urethral cancer |
| | | | | 10046433 | Urethral cancer metastatic |
| | | | | 10046435 | Urethral cancer recurrent |
| | | | | 10049722 | Metastases to bladder |
| | | | | 10050018 | Renal cancer metastatic |
| | | | | 10050513 | Metastatic renal cell carcinoma |
| | | | | 10051690 | Urinary bladder sarcoma |
| | | | | 10051948 | Renal adenoma |
| | | | | 10056251 | Metastases to urinary tract |
| | | | | 10057352 | Metastatic carcinoma of the bladder |
| | | | | 10061183 | Genitourinary tract neoplasm |
| | | | | 10061272 | Malignant urinary tract neoplasm |
| | | | | 10061396 | Urinary tract carcinoma in situ |
| | | | | 10061398 | Urinary tract neoplasm |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Broad BIcMQ 'Urinary tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)' | Urinary tract malignancy events (BIcMQ) | 40000010 | | 10061482 | Renal neoplasm |
| | | | | 10061872 | Non-renal cell carcinoma of kidney |
| | | | | 10062221 | Ureteral neoplasm |
| | | | | 10062223 | Urethral neoplasm |
| | | | | 10066749 | Bladder transitional cell carcinoma stage 0 |
| | | | | 10066750 | Bladder transitional cell carcinoma recurrent |
| | | | | 10066751 | Bladder transitional cell carcinoma stage I |
| | | | | 10066752 | Bladder transitional cell carcinoma stage IV |
| | | | | 10066753 | Bladder transitional cell carcinoma stage II |
| | | | | 10066754 | Bladder transitional cell carcinoma stage III |
| | | | | 10067943 | Hereditary papillary renal carcinoma |
| | | | | 10067944 | Hereditary leiomyomatosis renal cell carcinoma |
| | | | | 10067946 | Renal cell carcinoma |
| | | | | 10069359 | Leukaemic infiltration renal |
| | | | | 10070179 | Denys-Drash syndrome |
| | | | | 10071080 | Transitional cell carcinoma metastatic |
| | | | | 10071664 | Bladder transitional cell carcinoma metastatic |
| | | | | 10072793 | Urethral melanoma metastatic |
| | | | | 10073251 | Clear cell renal cell carcinoma |
| | | | | 10074419 | Malignant genitourinary tract neoplasm |
| | | | | 10077051 | Transitional cell carcinoma recurrent |
| | | | | 10077166 | Genitourinary melanoma |
| | | | | 10078341 | Neuroendocrine carcinoma of the bladder |
| | | | | 10078493 | Papillary renal cell carcinoma |
| | | | | 10080544 | Chromophobe renal cell carcinoma |
| | | | | 10081895 | Multilocular cystic nephroma |
| | | | | 10085663 | Clear cell papillary renal cell carcinoma |
| | | | | 10086817 | Malignant urinary tract neoplasm metastatic |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures (BIcMQ)' | Bone fracture events (BIcMQ) | 40000012 | | 10000397 | Acetabulum fracture |
| | | | | 10002544 | Ankle fracture |
| | | | | 10009245 | Clavicle fracture |
| | | | | 10009506 | Closed fracture manipulation |
| | | | | 10010149 | Complicated fracture |
| | | | | 10010214 | Compression fracture |
| | | | | 10015741 | External fixation of fracture |
| | | | | 10016042 | Facial bones fracture |
| | | | | 10016450 | Femoral neck fracture |
| | | | | 10016454 | Femur fracture |
| | | | | 10016667 | Fibula fracture |
| | | | | 10016747 | Flail chest |
| | | | | 10016970 | Foot fracture |
| | | | | 10016997 | Forearm fracture |
| | | | | 10017076 | Fracture |
| | | | | 10017081 | Fracture delayed union |
| | | | | 10017085 | Fracture malunion |
| | | | | 10017088 | Fracture nonunion |
| | | | | 10017107 | Fracture of clavicle due to birth trauma |
| | | | | 10017296 | Fractured maxilla elevation |
| | | | | 10017308 | Fractured sacrum |
| | | | | 10017310 | Fractured skull depressed |
| | | | | 10018720 | Greenstick fracture |
| | | | | 10019114 | Hand fracture |
| | | | | 10020100 | Hip fracture |
| | | | | 10020462 | Humerus fracture |
| | | | | 10021343 | Ilium fracture |
| | | | | 10022576 | Internal fixation of fracture |
| | | | | 10023149 | Jaw fracture |
| | | | | 10028200 | Multiple fractures |
| | | | | 10030527 | Open fracture |
| | | | | 10030682 | Open reduction of fracture |
| | | | | 10030684 | Open reduction of spinal fracture |
| | | | | 10031290 | Osteoporotic fracture |
| | | | | 10034122 | Patella fracture |
| | | | | 10034156 | Pathological fracture |
| | | | | 10037802 | Radius fracture |
| | | | | 10039117 | Rib fracture |
| | | | | 10039579 | Scapula fracture |
| | | | | 10040960 | Skull fractured base |
| | | | | 10041541 | Spinal compression fracture |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code Scope | Preferred term code | Preferred term |
|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures (BIcMQ)' | Bone fracture events (BIcMQ) | 40000012 | 10041569 | Spinal fracture |
| | | | 10042015 | Sternal fracture |
| | | | 10042212 | Stress fracture |
| | | | 10043827 | Tibia fracture |
| | | | 10045375 | Ulna fracture |
| | | | 10048049 | Wrist fracture |
| | | | 10048617 | Pseudarthrosis |
| | | | 10049164 | Fractured coccyx |
| | | | 10049514 | Traumatic fracture |
| | | | 10049946 | Cervical vertebral fracture |
| | | | 10049947 | Lumbar vertebral fracture |
| | | | 10049948 | Thoracic vertebral fracture |
| | | | 10052614 | Comminuted fracture |
| | | | 10053206 | Fracture displacement |
| | | | 10053962 | Epiphyseal fracture |
| | | | 10057147 | Fracture debridement |
| | | | 10057609 | Fracture reduction |
| | | | 10059362 | Fractured zygomatic arch elevation |
| | | | 10061161 | Pelvic fracture |
| | | | 10061365 | Skull fracture |
| | | | 10061394 | Upper limb fracture |
| | | | 10061599 | Lower limb fracture |
| | | | 10061959 | Fracture treatment |
| | | | 10064210 | Bone fissure |
| | | | 10064211 | Bone fragmentation |
| | | | 10066094 | Torus fracture |
| | | | 10066184 | Avulsion fracture |
| | | | 10066386 | Impacted fracture |
| | | | 10069066 | Intramedullary rod insertion |
| | | | 10069135 | Periprosthetic fracture |
| | | | 10069723 | Loss of anatomical alignment after fracture reduction |
| | | | 10070884 | Atypical femur fracture |
| | | | 10072132 | Fracture pain |
| | | | 10072395 | Atypical fracture |
| | | | 10073162 | Chance fracture |
| | | | 10073853 | Osteochondral fracture |
| | | | 10074362 | Sacroiliac fracture |
| | | | 10074551 | Limb fracture |
| | | | 10074807 | Spinal fusion fracture |
| | | | 10077270 | Surgical fixation of rib fracture |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures (BIcMQ)' | Bone fracture events (BIcMQ) | 40000012 | | 10077603 | Craniofacial fracture |
| | | | | 10078749 | Lisfranc fracture |
| | | | | 10079423 | Fracture blisters |
| | | | | 10079667 | Metaphyseal corner fracture |
| | | | | 10079813 | Fracture infection |
| | | | | 10079864 | Subchondral insufficiency fracture |
| | | | | 10080550 | Osteophyte fracture |
| | | | | 10081343 | Maisonneuve fracture |
| | | | | 10081442 | Stapes fracture |
| | | | | 10083585 | Skull fracture treatment |
| | | | | 10083586 | Spinal fracture treatment |
| | | | | 10085543 | Neurogenic fracture |
| | | | | 10085774 | Microfracture surgery |
| | | | | 10087273 | Depressed fracture |
| Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)' | Genital infections (BIcMQ) | 40000004 | | 10004055 | Bacterial vaginosis |
| | | | | 10004074 | Balanitis candida |
| | | | | 10004078 | Balanoposthitis |
| | | | | 10004138 | Bartholin's abscess |
| | | | | 10004142 | Bartholinitis |
| | | | | 10008323 | Cervicitis |
| | | | | 10014791 | Endometritis |
| | | | | 10015000 | Epididymitis |
| | | | | 10015001 | Epididymitis blastomyces |
| | | | | 10018143 | Genital candidiasis |
| | | | | 10020497 | Hydrocele male infected |
| | | | | 10030345 | Oophoritis |
| | | | | 10031064 | Orchitis |
| | | | | 10033119 | Ovarian abscess |
| | | | | 10033847 | Parametritis |
| | | | | 10034236 | Pelvic abscess |
| | | | | 10034254 | Pelvic inflammatory disease |
| | | | | 10034256 | Pelvic inflammatory disease mycoplasmal |
| | | | | 10034294 | Penile abscess |
| | | | | 10036934 | Prostatic abscess |
| | | | | 10036978 | Prostatitis |
| | | | | 10037651 | Pyometra |
| | | | | 10039453 | Salpingitis |
| | | | | 10039748 | Scrotal gangrene |
| | | | | 10039954 | Seminal vesiculitis |

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Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)' | Genital infections (BIcMQ) | 40000004 | | 10044250 | Toxic shock syndrome staphylococcal |
| | | | | 10044251 | Toxic shock syndrome streptococcal |
| | | | | 10046470 | Urethral stricture post infection |
| | | | | 10046914 | Vaginal infection |
| | | | | 10046957 | Vaginitis gardnerella |
| | | | | 10047732 | Vulval abscess |
| | | | | 10047752 | Vulval cellulitis |
| | | | | 10047780 | Vulvitis |
| | | | | 10047784 | Vulvovaginal candidiasis |
| | | | | 10047794 | Vulvovaginitis |
| | | | | 10048461 | Genital infection |
| | | | | 10049205 | Clitoris abscess |
| | | | | 10049571 | Scrotal abscess |
| | | | | 10049573 | Vaginal abscess |
| | | | | 10049677 | Salpingo-oophoritis |
| | | | | 10050428 | Fallopian tube abscess |
| | | | | 10050662 | Prostate infection |
| | | | | 10050739 | Erosive balanitis |
| | | | | 10051458 | Myometritis |
| | | | | 10051483 | Prostatovesiculitis |
| | | | | 10052301 | Vaginal cellulitis |
| | | | | 10052457 | Perineal abscess |
| | | | | 10053043 | Epididymitis ureaplasmal |
| | | | | 10054259 | Escherichia vaginitis |
| | | | | 10054824 | Tubo-ovarian abscess |
| | | | | 10056254 | Intrauterine infection |
| | | | | 10056345 | Rectovaginal septum abscess |
| | | | | 10056628 | Ovarian bacterial infection |
| | | | | 10057001 | Seminal vesicular infection |
| | | | | 10058674 | Pelvic infection |
| | | | | 10059070 | Pelvic sepsis |
| | | | | 10061179 | Genital infection bacterial |
| | | | | 10061180 | Genital infection fungal |
| | | | | 10061182 | Genitourinary tract infection |
| | | | | 10061912 | Penile infection |
| | | | | 10061977 | Genital infection female |
| | | | | 10062156 | Scrotal infection |
| | | | | 10062233 | Uterine infection |
| | | | | 10062316 | Genital abscess |
| | | | | 10062521 | Genital infection male |
| | | | | 10062707 | Parametric abscess |

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Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)' | Genital infections (BIcMQ) | 40000004 | | 10063012 | Uterine abscess |
| | | | | 10064501 | Spermatic cord funiculitis |
| | | | | 10064724 | Testicular abscess |
| | | | | 10064899 | Vulvovaginal mycotic infection |
| | | | | 10064929 | Cellulitis of male external genital organ |
| | | | | 10065583 | Urogenital infection bacterial |
| | | | | 10066876 | Perineal infection |
| | | | | 10067185 | Vulvovaginitis streptococcal |
| | | | | 10067236 | Cervicitis streptococcal |
| | | | | 10067320 | Prostatitis Escherichia coli |
| | | | | 10067741 | Balanoposthitis infective |
| | | | | 10068682 | Gangrenous balanitis |
| | | | | 10069918 | Bacterial prostatitis |
| | | | | 10071209 | Candida cervicitis |
| | | | | 10072020 | Pyospermia |
| | | | | 10074861 | Endometritis bacterial |
| | | | | 10074997 | Mycoplasma genitalium infection |
| | | | | 10075062 | Cervicitis mycoplasmal |
| | | | | 10075620 | Seminal vesicle abscess |
| | | | | 10078662 | Bacterial salpingitis |
| | | | | 10079520 | Vulvovaginitis staphylococcal |
| | | | | 10079521 | Fungal balanitis |
| | | | | 10079528 | Bacterial vulvovaginitis |
| | | | | 10081280 | Ureaplasmal vulvovaginitis |
| | | | | 10082162 | Ureaplasma cervicitis |
| | | | | 10083412 | Neovaginal infection |
| | | | | 10084348 | Scrotal cellulitis |
| | | | | 10085545 | Penile gangrene |
| Narrow BIcMQ 'Ketoacidosis (BIcMQ)' | Events indicative of ketoacidosis (BIcMQ) | 40000008 | | 10012668 | Diabetic hyperglycaemic coma |
| | | | | 10012671 | Diabetic ketoacidosis |
| | | | | 10012672 | Diabetic ketoacidotic hyperglycaemic coma |
| | | | | 10023379 | Ketoacidosis |
| | | | | 10080061 | Euglycaemic diabetic ketoacidosis |
| Narrow BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis' | Pyelonephritis or Urosepsis (BIcMQ) | 40000013 | | 10023424 | Kidney infection |

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Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis' | Pyelonephritis or Urosepsis (BIcMQ) | 40000013 | | 10034531 | Perinephric abscess |
| | | | | 10037584 | Pyelitis |
| | | | | 10037596 | Pyelonephritis |
| | | | | 10037597 | Pyelonephritis acute |
| | | | | 10037601 | Pyelonephritis chronic |
| | | | | 10037603 | Pyelonephritis mycoplasmal |
| | | | | 10037653 | Pyonephrosis |
| | | | | 10038351 | Renal abscess |
| | | | | 10048709 | Urosepsis |
| | | | | 10049100 | Pyelocystitis |
| | | | | 10058596 | Renal cyst infection |
| | | | | 10059517 | Bacterial pyelonephritis |
| | | | | 10065214 | Pyelonephritis fungal |
| | | | | 10068822 | Emphysematous pyelonephritis |
| | | | | 10072058 | Perinephritis |
| | | | | 10074409 | Escherichia pyelonephritis |
| | | | | 10078229 | Renal graft infection |
| | | | | 10082040 | Nephritis bacterial |
| | | | | 10084121 | Infected urinoma |
| Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)' | Urinary tract infections (BIcMQ) | 40000002 | | 10004056 | Bacteriuria |
| | | | | 10004058 | Bacteriuria in pregnancy |
| | | | | 10011781 | Cystitis |
| | | | | 10011790 | Cystitis escherichia |
| | | | | 10011792 | Cystitis gonococcal |
| | | | | 10011793 | Cystitis haemorrhagic |
| | | | | 10011797 | Cystitis klebsiella |
| | | | | 10011799 | Cystitis pseudomonal |
| | | | | 10017525 | Fungal cystitis |
| | | | | 10023424 | Kidney infection |
| | | | | 10034531 | Perinephric abscess |
| | | | | 10037584 | Pyelitis |
| | | | | 10037596 | Pyelonephritis |
| | | | | 10037597 | Pyelonephritis acute |
| | | | | 10037601 | Pyelonephritis chronic |
| | | | | 10037603 | Pyelonephritis mycoplasmal |
| | | | | 10037653 | Pyonephrosis |
| | | | | 10038351 | Renal abscess |
| | | | | 10046424 | Urethral abscess |
| | | | | 10046470 | Urethral stricture post infection |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)' | Urinary tract infections (BIcMQ) | 40000002 | | 10046480 | Urethritis |
| | | | | 10046482 | Urethritis chlamydial |
| | | | | 10046483 | Urethritis gonococcal |
| | | | | 10046489 | Urethritis trichomonal |
| | | | | 10046490 | Urethritis ureaplasmal |
| | | | | 10046571 | Urinary tract infection |
| | | | | 10046572 | Urinary tract infection enterococcal |
| | | | | 10046573 | Urinary tract infection neonatal |
| | | | | 10046704 | Urogenital trichomoniasis |
| | | | | 10048709 | Urosepsis |
| | | | | 10049059 | Urinary tract infection fungal |
| | | | | 10049100 | Pyelocystitis |
| | | | | 10051250 | Ureteritis |
| | | | | 10051959 | Urinary bladder abscess |
| | | | | 10052238 | Escherichia urinary tract infection |
| | | | | 10052299 | Urethral carbuncle |
| | | | | 10054088 | Urinary tract infection bacterial |
| | | | | 10056351 | Emphysematous cystitis |
| | | | | 10056396 | Asymptomatic bacteriuria |
| | | | | 10058523 | Bladder candidiasis |
| | | | | 10058596 | Renal cyst infection |
| | | | | 10059517 | Bacterial pyelonephritis |
| | | | | 10061181 | Genitourinary tract gonococcal infection |
| | | | | 10061395 | Ureter abscess |
| | | | | 10062279 | Urinary tract infection pseudomonal |
| | | | | 10062280 | Urinary tract infection staphylococcal |
| | | | | 10064850 | Cystitis erosive |
| | | | | 10065198 | Cystitis bacterial |
| | | | | 10065214 | Pyelonephritis fungal |
| | | | | 10065582 | Urogenital infection fungal |
| | | | | 10065583 | Urogenital infection bacterial |
| | | | | 10066757 | Urinary tract abscess |
| | | | | 10068822 | Emphysematous pyelonephritis |
| | | | | 10070300 | Streptococcal urinary tract infection |
| | | | | 10072058 | Perinephritis |
| | | | | 10074409 | Escherichia pyelonephritis |
| | | | | 10074457 | Bladder diverticulitis |
| | | | | 10075063 | Urethritis mycoplasmal |
| | | | | 10077375 | Funguria |
| | | | | 10078229 | Renal graft infection |
| | | | | 10078665 | Bacterial urethritis |

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Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)' | Urinary tract infections (BIcMQ) | 40000002 | | 10078666 | Bacterial ureteritis |
| | | | | 10081163 | Fungal urethritis |
| | | | | 10081185 | Gonococcal infection |
| | | | | 10081262 | Candida urethritis |
| | | | | 10082040 | Nephritis bacterial |
| | | | | 10082818 | Providencia urinary tract infection |
| | | | | 10083162 | Urinary tract candidiasis |
| | | | | 10083524 | Campylobacter urinary tract infection |
| | | | | 10084121 | Infected urinoma |
| | | | | 10084826 | Aerococcus urinae infection |
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)' | Volume depletion events (BIcMQ) | 40000006 | | 10005731 | Blood pressure ambulatory decreased |
| | | | | 10005734 | Blood pressure decreased |
| | | | | 10005737 | Blood pressure diastolic decreased |
| | | | | 10005758 | Blood pressure systolic decreased |
| | | | | 10009192 | Circulatory collapse |
| | | | | 10012174 | Dehydration |
| | | | | 10021097 | Hypotension |
| | | | | 10021137 | Hypovolaemia |
| | | | | 10021138 | Hypovolaemic shock |
| | | | | 10026983 | Mean arterial pressure decreased |
| | | | | 10031127 | Orthostatic hypotension |
| | | | | 10036653 | Presyncope |
| | | | | 10042772 | Syncope |
| | | | | 10053356 | Blood pressure orthostatic decreased |
| | | | | 10066077 | Diastolic hypotension |
| | | | | 10078280 | CT hypotension complex |
| | | | | 10083659 | Hypotensive crisis |
| | | | | 10084012 | Dialysis hypotension |
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)' excluding PTs 'Dehydration' and 'Hypovolaemia' | Hypotension events (BIcMQ) | 40000001 | | 10005731 | Blood pressure ambulatory decreased |
| | | | | 10005734 | Blood pressure decreased |
| | | | | 10005737 | Blood pressure diastolic decreased |
| | | | | 10005758 | Blood pressure systolic decreased |
| | | | | 10009192 | Circulatory collapse |
| | | | | 10021097 | Hypotension |
| | | | | 10021138 | Hypovolaemic shock |

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Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)' excluding PTs 'Dehydration' and 'Hypovolaemia' | Hypotension events (BIcMQ) | 40000001 | | 10026983 | Mean arterial pressure decreased |
| | | | | 10031127 | Orthostatic hypotension |
| | | | | 10036653 | Presyncope |
| | | | | 10042772 | Syncope |
| | | | | 10053356 | Blood pressure orthostatic decreased |
| | | | | 10066077 | Diastolic hypotension |
| | | | | 10078280 | CT hypotension complex |
| | | | | 10083659 | Hypotensive crisis |
| | | | | 10084012 | Dialysis hypotension |
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10000804 | Acute hepatic failure |
| | | | | 10001547 | Alanine aminotransferase abnormal |
| | | | | 10001551 | Alanine aminotransferase increased |
| | | | | 10001942 | Ammonia abnormal |
| | | | | 10001946 | Ammonia increased |
| | | | | 10003445 | Ascites |
| | | | | 10003477 | Aspartate aminotransferase abnormal |
| | | | | 10003481 | Aspartate aminotransferase increased |
| | | | | 10003547 | Asterixis |
| | | | | 10003827 | Autoimmune hepatitis |
| | | | | 10004659 | Biliary cirrhosis |
| | | | | 10004664 | Biliary fibrosis |
| | | | | 10004685 | Bilirubin conjugated increased |
| | | | | 10004792 | Biopsy liver abnormal |
| | | | | 10005364 | Blood bilirubin increased |
| | | | | 10005370 | Blood bilirubin unconjugated increased |
| | | | | 10006408 | Bromosulphthalein test abnormal |
| | | | | 10008635 | Cholestasis |
| | | | | 10008909 | Chronic hepatitis |
| | | | | 10010075 | Coma hepatic |
| | | | | 10017688 | Gamma-glutamyltransferase abnormal |
| | | | | 10017693 | Gamma-glutamyltransferase increased |
| | | | | 10019621 | Hepaplastin abnormal |
| | | | | 10019622 | Hepaplastin decreased |

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Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10019637 | Hepatic atrophy |
| | | | | 10019641 | Hepatic cirrhosis |
| | | | | 10019660 | Hepatic encephalopathy |
| | | | | 10019663 | Hepatic failure |
| | | | | 10019668 | Hepatic fibrosis |
| | | | | 10019670 | Hepatic function abnormal |
| | | | | 10019692 | Hepatic necrosis |
| | | | | 10019705 | Hepatic pain |
| | | | | 10019708 | Hepatic steatosis |
| | | | | 10019717 | Hepatitis |
| | | | | 10019727 | Hepatitis acute |
| | | | | 10019754 | Hepatitis cholestatic |
| | | | | 10019755 | Hepatitis chronic active |
| | | | | 10019759 | Hepatitis chronic persistent |
| | | | | 10019772 | Hepatitis fulminant |
| | | | | 10019795 | Hepatitis toxic |
| | | | | 10019837 | Hepatocellular injury |
| | | | | 10019842 | Hepatomegaly |
| | | | | 10019845 | Hepatorenal failure |
| | | | | 10019846 | Hepatorenal syndrome |
| | | | | 10019847 | Hepatosplenomegaly |
| | | | | 10019851 | Hepatotoxicity |
| | | | | 10020575 | Hyperammonaemia |
| | | | | 10020578 | Hyperbilirubinaemia |
| | | | | 10021209 | Icterus index increased |
| | | | | 10023025 | Ischaemic hepatitis |
| | | | | 10023126 | Jaundice |
| | | | | 10023129 | Jaundice cholestatic |
| | | | | 10023136 | Jaundice hepatocellular |
| | | | | 10023321 | Kayser-Fleischer ring |
| | | | | 10024670 | Liver disorder |
| | | | | 10024690 | Liver function test abnormal |
| | | | | 10024712 | Liver tenderness |
| | | | | 10024714 | Liver transplant |
| | | | | 10025129 | Lupoid hepatic cirrhosis |
| | | | | 10029530 | Non-alcoholic fatty liver |
| | | | | 10030210 | Oesophageal varices haemorrhage |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10036200 | Portal hypertension |
| | | | | 10039012 | Reye's syndrome |
| | | | | 10045428 | Ultrasound liver abnormal |
| | | | | 10048611 | Cholaemia |
| | | | | 10049199 | Hepatic cytolysis |
| | | | | 10049631 | Oedema due to hepatic disease |
| | | | | 10050792 | Urine bilirubin increased |
| | | | | 10050897 | Portal hypertensive gastropathy |
| | | | | 10051010 | Duodenal varices |
| | | | | 10051012 | Gastric varices |
| | | | | 10051015 | Radiation hepatitis |
| | | | | 10051081 | Nodular regenerative hyperplasia |
| | | | | 10051333 | Guanase increased |
| | | | | 10051343 | Bile output decreased |
| | | | | 10051344 | Bile output abnormal |
| | | | | 10051924 | Hypercholia |
| | | | | 10052274 | Hepatopulmonary syndrome |
| | | | | 10052279 | Renal and liver transplant |
| | | | | 10052550 | Liver induration |
| | | | | 10052554 | Foetor hepaticus |
| | | | | 10053219 | Non-alcoholic steatohepatitis |
| | | | | 10053244 | Hepatocellular foamy cell syndrome |
| | | | | 10054125 | Perihepatic discomfort |
| | | | | 10054889 | Transaminases increased |
| | | | | 10056091 | Varices oesophageal |
| | | | | 10056536 | X-ray hepatobiliary abnormal |
| | | | | 10056956 | Subacute hepatic failure |
| | | | | 10057110 | Hepatic mass |
| | | | | 10057572 | Gastric varices haemorrhage |
| | | | | 10057573 | Chronic hepatic failure |
| | | | | 10058117 | Ocular icterus |
| | | | | 10058477 | Blood bilirubin abnormal |
| | | | | 10059710 | Galactose elimination capacity test abnormal |
| | | | | 10059712 | Galactose elimination capacity test decreased |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10060107 | Liver-kidney microsomal antibody positive |
| | | | | 10060794 | Hepatic enzyme decreased |
| | | | | 10060795 | Hepatic enzyme increased |
| | | | | 10061009 | Bilirubin excretion disorder |
| | | | | 10061135 | Spontaneous bacterial peritonitis |
| | | | | 10061947 | Liver scan abnormal |
| | | | | 10061997 | Hepatectomy |
| | | | | 10061998 | Hepatic lesion |
| | | | | 10062000 | Hepatobiliary disease |
| | | | | 10062040 | Liver operation |
| | | | | 10062685 | Hepatic enzyme abnormal |
| | | | | 10062688 | Transaminases abnormal |
| | | | | 10063075 | Cryptogenic cirrhosis |
| | | | | 10064190 | Cholestatic pruritus |
| | | | | 10064558 | Total bile acids increased |
| | | | | 10064668 | Hepatic infiltration eosinophilic |
| | | | | 10064676 | Graft versus host disease in liver |
| | | | | 10064712 | Mitochondrial aspartate aminotransferase increased |
| | | | | 10065274 | Hepatic calcification |
| | | | | 10066195 | Hepatobiliary scan abnormal |
| | | | | 10066244 | Hepatic sequestration |
| | | | | 10066263 | Acute graft versus host disease in liver |
| | | | | 10066597 | Gastrooesophageal variceal haemorrhage prophylaxis |
| | | | | 10066599 | Hepatic encephalopathy prophylaxis |
| | | | | 10066758 | Mixed liver injury |
| | | | | 10066869 | Molar ratio of total branched-chain amino acid to tyrosine |
| | | | | 10067125 | Liver injury |
| | | | | 10067281 | Portopulmonary hypertension |
| | | | | 10067338 | Retrograde portal vein flow |
| | | | | 10067365 | Hepatic hydrothorax |
| | | | | 10067718 | Bilirubin conjugated abnormal |
| | | | | 10067737 | Lupus hepatitis |
| | | | | 10067823 | Splenic varices |
| | | | | 10067969 | Cholestatic liver injury |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10068237 | Hypertransaminasaemia |
| | | | | 10068287 | Child-Pugh-Turcotte score increased |
| | | | | 10068358 | Hepatic vascular resistance increased |
| | | | | 10068547 | Bacterascites |
| | | | | 10068662 | Splenic varices haemorrhage |
| | | | | 10068923 | Portal hypertensive enteropathy |
| | | | | 10068997 | Hepatic artery flow decreased |
| | | | | 10070815 | Acute yellow liver atrophy |
| | | | | 10070953 | Reynold's syndrome |
| | | | | 10071198 | Allergic hepatitis |
| | | | | 10071265 | Diabetic hepatopathy |
| | | | | 10071502 | Intestinal varices |
| | | | | 10072160 | Chronic graft versus host disease in liver |
| | | | | 10072268 | Drug-induced liver injury |
| | | | | 10072284 | Varicose veins of abdominal wall |
| | | | | 10072319 | Gallbladder varices |
| | | | | 10073209 | Portal vein dilatation |
| | | | | 10073215 | Peripancreatic varices |
| | | | | 10073979 | Portal vein cavernous transformation |
| | | | | 10074150 | Biliary ascites |
| | | | | 10074151 | Parenteral nutrition associated liver disease |
| | | | | 10074726 | Portal fibrosis |
| | | | | 10075895 | Liver palpable |
| | | | | 10076237 | Gastric variceal injection |
| | | | | 10076238 | Gastric variceal ligation |
| | | | | 10076254 | Hepatic hypertrophy |
| | | | | 10076331 | Steatohepatitis |
| | | | | 10076640 | Liver dialysis |
| | | | | 10077020 | Child-Pugh-Turcotte score abnormal |
| | | | | 10077215 | Hepatic steato-fibrosis |
| | | | | 10077259 | Non-cirrhotic portal hypertension |
| | | | | 10077305 | Acute on chronic liver failure |
| | | | | 10077356 | Bilirubin urine present |
| | | | | 10077677 | Liver function test decreased |
| | | | | 10077692 | Liver function test increased |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10078058 | Intestinal varices haemorrhage |
| | | | | 10078360 | Computerised tomogram liver abnormal |
| | | | | 10078438 | White nipple sign |
| | | | | 10078962 | Immune-mediated hepatitis |
| | | | | 10079446 | Portal hypertensive colopathy |
| | | | | 10080429 | Primary biliary cholangitis |
| | | | | 10080576 | Alloimmune hepatitis |
| | | | | 10080679 | Regenerative siderotic hepatic nodule |
| | | | | 10080860 | Acquired hepatocerebral degeneration |
| | | | | 10082443 | Magnetic resonance proton density fat fraction measurement |
| | | | | 10082480 | Cardiohepatic syndrome |
| | | | | 10082832 | AST/ALT ratio abnormal |
| | | | | 10083010 | Sugiura procedure |
| | | | | 10083171 | Hepatic venous pressure gradient increased |
| | | | | 10083172 | Hepatic venous pressure gradient abnormal |
| | | | | 10083406 | Immune-mediated cholangitis |
| | | | | 10083521 | Immune-mediated hepatic disorder |
| | | | | 10084058 | Congestive hepatopathy |
| | | | | 10084751 | Hepatic hypoperfusion |
| | | | | 10084797 | Flood syndrome |
| | | | | 10085121 | Magnetic resonance imaging hepatobiliary abnormal |
| | | | | 10086006 | Acquired factor V deficiency |
| | | | | 10086970 | Anti-liver cytosol antibody type 1 positive |
| | | | | 10087030 | Omental oedema |
| PTs 'Gout', 'Gouty arthritis', 'Gouty tophus' | Gout (user-defined) | 40000032 | | 10018627 | Gout |
| | | | | 10018634 | Gouty arthritis |
| | | | | 10018641 | Gouty tophus |
| PTs 'Hyperkalaemia', 'Blood potassium increased' | Hyperkalaemia (user-defined) | 40000021 | | 10005725 | Blood potassium increased |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.2.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| PTs 'Hyperkalaemia', 'Blood potassium increased' | Hyperkalaemia (user-defined) | 40000021 | | 10020646 | Hyperkalaemia |
| SMQ 'Acute renal failure' | Acute renal failure (SMQ) | 20000003 | Narrow | 10002847 | Anuria |
| | | | | 10003885 | Azotaemia |
| | | | | 10018875 | Haemodialysis |
| | | | | 10029155 | Nephropathy toxic |
| | | | | 10030302 | Oliguria |
| | | | | 10034660 | Peritoneal dialysis |
| | | | | 10038435 | Renal failure |
| | | | | 10038447 | Renal failure neonatal |
| | | | | 10049776 | Renal impairment neonatal |
| | | | | 10049778 | Neonatal anuria |
| | | | | 10053090 | Haemofiltration |
| | | | | 10061105 | Dialysis |
| | | | | 10062237 | Renal impairment |
| | | | | 10066338 | Continuous haemodiafiltration |
| | | | | 10069339 | Acute kidney injury |
| | | | | 10069688 | Acute phosphate nephropathy |
| | | | | 10072370 | Prerenal failure |
| | | | | 10078987 | Foetal renal impairment |
| | | | | 10081980 | Subacute kidney injury |
| SMQ 'Hypoglycaemia' | Hypoglycaemic events (SMQ) | 20000226 | Narrow | 10005555 | Blood glucose decreased |
| | | | | 10020993 | Hypoglycaemia |
| | | | | 10020994 | Hypoglycaemia neonatal |
| | | | | 10020997 | Hypoglycaemia unawareness |
| | | | | 10021000 | Hypoglycaemic coma |
| | | | | 10021002 | Hypoglycaemic encephalopathy |
| | | | | 10040576 | Shock hypoglycaemic |
| | | | | 10048803 | Hypoglycaemic seizure |
| | | | | 10054998 | Neuroglycopenia |
| | | | | 10059035 | Postprandial hypoglycaemia |
| | | | | 10065981 | Hypoglycaemic unconsciousness |
| | | | | 10077216 | Hyperinsulinaemic hypoglycaemia |
| | | | | 10080024 | Nesidioblastosis |
| | | | | 10082152 | Paraneoplastic hypoglycaemia |
| | | | | 10082172 | Glycopenia |

Analyses are based on 1245.110 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

**R.3**

**R.3.1**

**R.3.1.1**

**R.3.1.1.1**

R.3.1.1.1.1 Time to all-cause mortality

Table R.3.1.1.1.1: 1 Cox Regression for time to all-cause mortality until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 210 | 16.5 | 12.43 | 1278 | 184 | 14.4 | 10.81 | 0.85 | (0.70,1.04) | 0.1072 | |
| Sex | | | | | | | | | | | | 0.4751 |
| Male | 959 | 161 | 16.8 | 12.57 | 975 | 149 | 15.3 | 11.46 | 0.88 | (0.71,1.10) | 0.2716 | |
| Female | 317 | 49 | 15.5 | 11.99 | 303 | 35 | 11.6 | 8.69 | 0.74 | (0.48,1.14) | 0.1712 | |
| Age [years] | | | | | | | | | | | | 0.8589 |
| <65 | 436 | 55 | 12.6 | 9.49 | 392 | 42 | 10.7 | 8.09 | 0.88 | (0.59,1.31) | 0.5206 | |
| >=65 | 840 | 155 | 18.5 | 13.96 | 886 | 142 | 16.0 | 11.99 | 0.84 | (0.67,1.06) | 0.1351 | |
| Region | | | | | | | | | | | | 0.4367 |
| North America | 161 | 33 | 20.5 | 14.71 | 159 | 32 | 20.1 | 13.60 | 0.89 | (0.55,1.45) | 0.6471 | |
| Latin America | 420 | 66 | 15.7 | 12.95 | 440 | 69 | 15.7 | 12.94 | 0.97 | (0.69,1.36) | 0.8410 | |
| Europe | 471 | 81 | 17.2 | 12.66 | 467 | 60 | 12.8 | 9.40 | 0.75 | (0.54,1.05) | 0.0897 | |
| Asia | 174 | 22 | 12.6 | 8.79 | 165 | 21 | 12.7 | 8.97 | 1.01 | (0.55,1.84) | 0.9770 | |
| Other | 50 | 8 | 16.0 | 12.20 | 47 | 2 | 4.3 | 3.22 | 0.25 | (0.05,1.20) | 0.0835 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3931 |
| Diabetic | 696 | 123 | 17.7 | 13.21 | 698 | 112 | 16.0 | 12.13 | 0.91 | (0.71,1.18) | 0.4833 | |
| Non-Diabetic | 580 | 87 | 15.0 | 11.47 | 580 | 72 | 12.4 | 9.24 | 0.77 | (0.56,1.05) | 0.0934 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5886 |
| <30 | 890 | 156 | 17.5 | 13.04 | 836 | 121 | 14.5 | 10.90 | 0.83 | (0.65,1.05) | 0.1143 | |
| >=30 | 386 | 54 | 14.0 | 10.93 | 442 | 63 | 14.3 | 10.63 | 0.93 | (0.65,1.34) | 0.6993 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7687 |
| <130 | 859 | 154 | 17.9 | 13.67 | 834 | 128 | 15.3 | 11.74 | 0.84 | (0.66,1.06) | 0.1468 | |
| >=130 | 417 | 56 | 13.4 | 9.94 | 444 | 56 | 12.6 | 9.14 | 0.90 | (0.62,1.30) | 0.5694 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4617 |
| <75 | 720 | 136 | 18.9 | 14.29 | 678 | 117 | 17.3 | 13.21 | 0.91 | (0.71,1.16) | 0.4400 | |
| 75 to <85 | 348 | 48 | 13.8 | 10.36 | 382 | 49 | 12.8 | 9.52 | 0.89 | (0.60,1.33) | 0.5753 | |
| >=85 | 208 | 26 | 12.5 | 9.46 | 218 | 18 | 8.3 | 5.95 | 0.60 | (0.33,1.10) | 0.0996 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.3.1.1.1.1: 1 Cox Regression for time to all-cause mortality until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.7767 |
| <30 | 90 | 25 | 27.8 | 23.79 | 115 | 27 | 23.5 | 17.62 | 0.72 | (0.42,1.25) | 0.2472 | |
| 30 to <45 | 349 | 59 | 16.9 | 12.69 | 345 | 53 | 15.4 | 11.57 | 0.92 | (0.63,1.33) | 0.6410 | |
| >=45 | 837 | 126 | 15.1 | 11.25 | 818 | 104 | 12.7 | 9.53 | 0.82 | (0.63,1.07) | 0.1441 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0695 |
| Normal (<30) | 452 | 64 | 14.2 | 10.78 | 456 | 50 | 11.0 | 7.99 | 0.73 | (0.50,1.06) | 0.0975 | |
| Microalbuminuria (30 to <=300) | 628 | 115 | 18.3 | 13.84 | 608 | 88 | 14.5 | 10.94 | 0.79 | (0.59,1.04) | 0.0895 | |
| Macroalbuminuria (>300) | 189 | 28 | 14.8 | 10.93 | 207 | 45 | 21.7 | 16.97 | 1.41 | (0.88,2.26) | 0.1551 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2937 |
| Low, moderate or high | 953 | 145 | 15.2 | 11.49 | 947 | 119 | 12.6 | 9.41 | 0.80 | (0.62,1.02) | 0.0662 | |
| Very high | 317 | 63 | 19.9 | 14.96 | 325 | 65 | 20.0 | 15.04 | 1.00 | (0.71,1.41) | 0.9965 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7011 |
| No | 161 | 33 | 20.5 | 15.07 | 168 | 30 | 17.9 | 12.87 | 0.77 | (0.47,1.27) | 0.3142 | |
| Yes | 1115 | 177 | 15.9 | 12.03 | 1110 | 154 | 13.9 | 10.48 | 0.86 | (0.69,1.07) | 0.1771 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.8181 |
| No | 62 | 14 | 22.6 | 17.15 | 72 | 14 | 19.4 | 15.42 | 0.92 | (0.44,1.94) | 0.8326 | |
| Yes | 1214 | 196 | 16.1 | 12.19 | 1206 | 170 | 14.1 | 10.55 | 0.84 | (0.69,1.04) | 0.1040 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.8965 |
| No | 46 | 3 | 6.5 | 4.83 | 57 | 3 | 5.3 | 3.90 | 0.77 | (0.15,3.82) | 0.7478 | |
| Yes | 1230 | 207 | 16.8 | 12.72 | 1221 | 181 | 14.8 | 11.13 | 0.86 | (0.70,1.04) | 0.1264 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.1.1: 1**

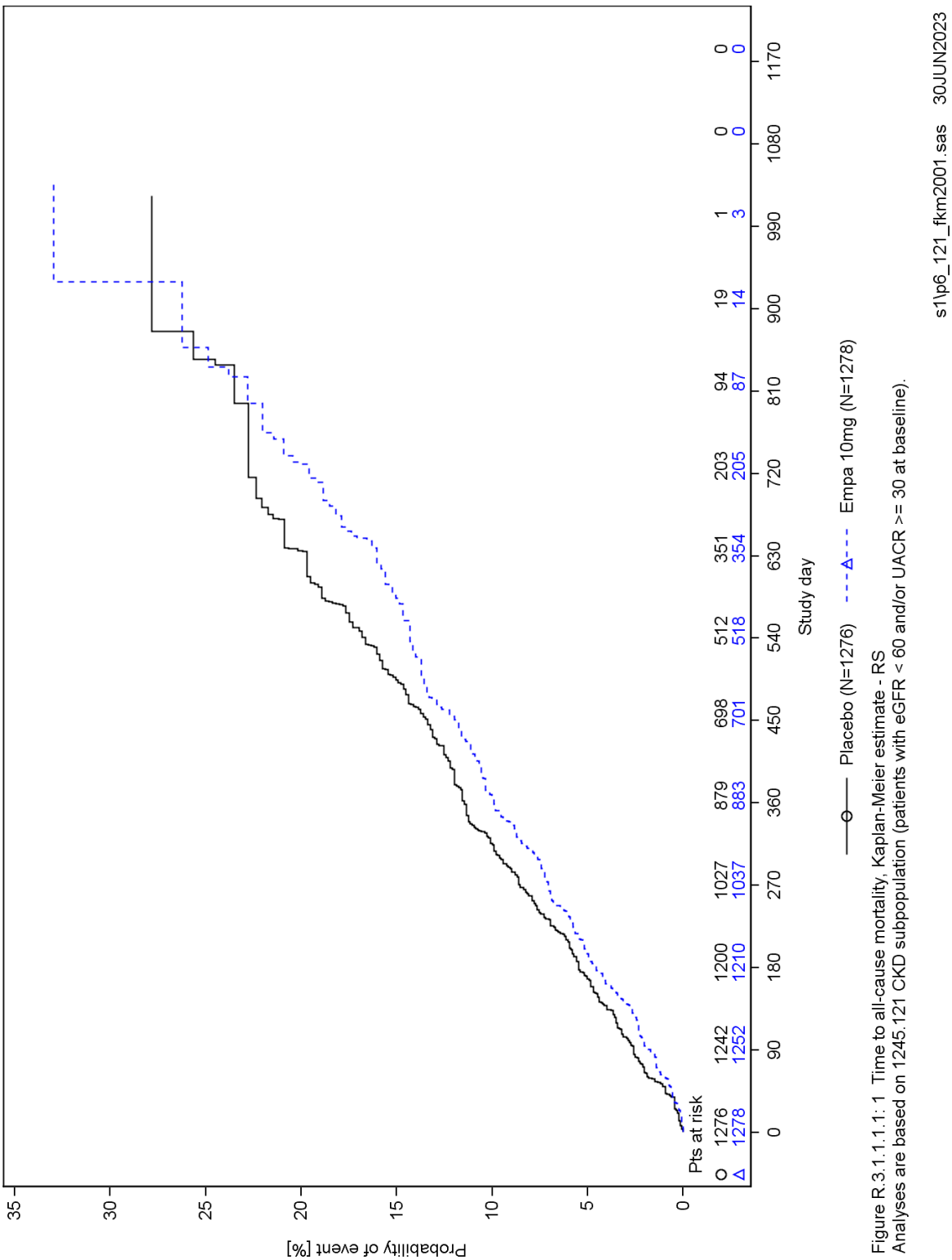


Figure R.3.1.1.1.1: 1 Time to all-cause mortality, Kaplan-Meier estimate - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.3.1.1.1.2**

R.3.1.1.1.2 Time to adjudicated CV death

Table R.3.1.1.1.2: 1 Cox Regression for time to adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 157 | 12.3 | 9.29 | 1278 | 130 | 10.2 | 7.63 | 0.81 | (0.64,1.02) | 0.0797 | |
| Sex | | | | | | | | | | | | 0.1212 |
| Male | 959 | 115 | 12.0 | 8.98 | 975 | 107 | 11.0 | 8.23 | 0.90 | (0.69,1.17) | 0.4208 | |
| Female | 317 | 42 | 13.2 | 10.27 | 303 | 23 | 7.6 | 5.71 | 0.57 | (0.34,0.95) | 0.0305 | |
| Age [years] | | | | | | | | | | | | 0.8441 |
| <65 | 436 | 48 | 11.0 | 8.29 | 392 | 33 | 8.4 | 6.36 | 0.78 | (0.50,1.22) | 0.2772 | |
| >=65 | 840 | 109 | 13.0 | 9.82 | 886 | 97 | 10.9 | 8.19 | 0.82 | (0.63,1.08) | 0.1659 | |
| Region | | | | | | | | | | | | 0.7029 |
| North America | 161 | 18 | 11.2 | 8.02 | 159 | 16 | 10.1 | 6.80 | 0.84 | (0.43,1.65) | 0.6141 | |
| Latin America | 420 | 52 | 12.4 | 10.20 | 440 | 47 | 10.7 | 8.81 | 0.85 | (0.57,1.26) | 0.4120 | |
| Europe | 471 | 58 | 12.3 | 9.07 | 467 | 48 | 10.3 | 7.52 | 0.83 | (0.57,1.22) | 0.3414 | |
| Asia | 174 | 21 | 12.1 | 8.39 | 165 | 17 | 10.3 | 7.26 | 0.85 | (0.45,1.62) | 0.6306 | |
| Other | 50 | 8 | 16.0 | 12.20 | 47 | 2 | 4.3 | 3.22 | 0.26 | (0.06,1.22) | 0.0874 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.7434 |
| Diabetic | 696 | 91 | 13.1 | 9.77 | 698 | 76 | 10.9 | 8.23 | 0.84 | (0.62,1.14) | 0.2599 | |
| Non-Diabetic | 580 | 66 | 11.4 | 8.70 | 580 | 54 | 9.3 | 6.93 | 0.78 | (0.54,1.11) | 0.1670 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5298 |
| <30 | 890 | 118 | 13.3 | 9.87 | 836 | 86 | 10.3 | 7.75 | 0.78 | (0.59,1.03) | 0.0803 | |
| >=30 | 386 | 39 | 10.1 | 7.90 | 442 | 44 | 10.0 | 7.42 | 0.92 | (0.60,1.42) | 0.7039 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5812 |
| <130 | 859 | 116 | 13.5 | 10.30 | 834 | 89 | 10.7 | 8.17 | 0.79 | (0.60,1.04) | 0.0863 | |
| >=130 | 417 | 41 | 9.8 | 7.28 | 444 | 41 | 9.2 | 6.69 | 0.91 | (0.59,1.40) | 0.6609 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.9118 |
| <75 | 720 | 98 | 13.6 | 10.30 | 678 | 78 | 11.5 | 8.81 | 0.85 | (0.63,1.15) | 0.2937 | |
| 75 to <85 | 348 | 41 | 11.8 | 8.85 | 382 | 37 | 9.7 | 7.19 | 0.80 | (0.51,1.25) | 0.3219 | |
| >=85 | 208 | 18 | 8.7 | 6.55 | 218 | 15 | 6.9 | 4.96 | 0.73 | (0.37,1.45) | 0.3722 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.3.1.1.1.2: 1 Cox Regression for time to adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4420 |
| <30 | 90 | 18 | 20.0 | 17.13 | 115 | 15 | 13.0 | 9.79 | 0.57 | (0.28,1.12) | 0.1032 | |
| 30 to <45 | 349 | 44 | 12.6 | 9.47 | 345 | 41 | 11.9 | 8.95 | 0.95 | (0.62,1.46) | 0.8202 | |
| >=45 | 837 | 95 | 11.4 | 8.48 | 818 | 74 | 9.0 | 6.78 | 0.79 | (0.58,1.07) | 0.1249 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0505 |
| Normal (<30) | 452 | 44 | 9.7 | 7.41 | 456 | 33 | 7.2 | 5.28 | 0.71 | (0.45,1.11) | 0.1356 | |
| Microalbuminuria (30 to <=300) | 628 | 92 | 14.6 | 11.07 | 608 | 63 | 10.4 | 7.83 | 0.71 | (0.52,0.98) | 0.0383 | |
| Macroalbuminuria (>300) | 189 | 19 | 10.1 | 7.41 | 207 | 33 | 15.9 | 12.44 | 1.55 | (0.88,2.73) | 0.1305 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5381 |
| Low, moderate or high | 953 | 108 | 11.3 | 8.56 | 947 | 86 | 9.1 | 6.80 | 0.78 | (0.59,1.04) | 0.0907 | |
| Very high | 317 | 47 | 14.8 | 11.16 | 325 | 44 | 13.5 | 10.18 | 0.92 | (0.61,1.38) | 0.6761 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5391 |
| No | 161 | 26 | 16.1 | 11.87 | 168 | 20 | 11.9 | 8.58 | 0.68 | (0.38,1.23) | 0.2049 | |
| Yes | 1115 | 131 | 11.7 | 8.91 | 1110 | 110 | 9.9 | 7.48 | 0.84 | (0.65,1.08) | 0.1677 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9251 |
| No | 62 | 10 | 16.1 | 12.25 | 72 | 9 | 12.5 | 9.91 | 0.85 | (0.34,2.09) | 0.7169 | |
| Yes | 1214 | 147 | 12.1 | 9.14 | 1206 | 121 | 10.0 | 7.51 | 0.81 | (0.64,1.03) | 0.0847 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.6847 |
| No | 46 | 3 | 6.5 | 4.83 | 57 | 2 | 3.5 | 2.60 | 0.56 | (0.09,3.39) | 0.5309 | |
| Yes | 1230 | 154 | 12.5 | 9.46 | 1221 | 128 | 10.5 | 7.87 | 0.82 | (0.65,1.04) | 0.0973 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.1.2: 1**

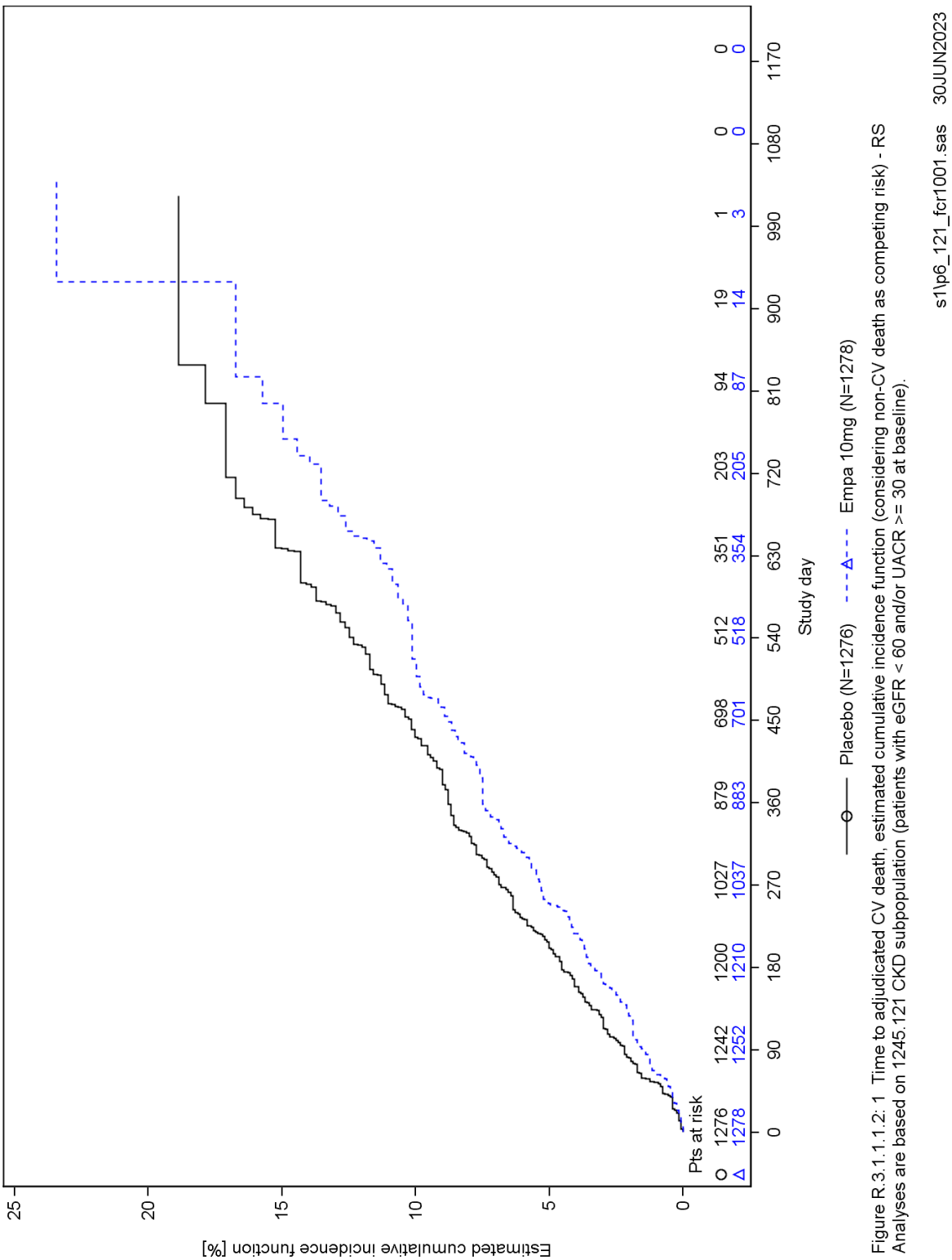


Figure R.3.1.1.1.2: 1 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.3.1.1.1.3**

R.3.1.1.1.3 Time to adjudicated renal death

Table R.3.1.1.1.3: 1 Cox Regression for time to adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 2 | 0.2 | 0.12 | 1278 | 2 | 0.2 | 0.12 | 0.95 | (0.13,7.00) | 0.9624 | |
| Sex | | | | | | | | | | | | |
| Male | 959 | 2 | 0.2 | 0.16 | 975 | 2 | 0.2 | 0.15 | | | | |
| Female | 317 | 0 | 0 | 0.00 | 303 | 0 | 0 | 0.00 | | | | |
| Age [years] | | | | | | | | | | | | |
| <65 | 436 | 1 | 0.2 | 0.17 | 392 | 0 | 0 | 0.00 | | | | |
| >=65 | 840 | 1 | 0.1 | 0.09 | 886 | 2 | 0.2 | 0.17 | | | | |
| Region | | | | | | | | | | | | |
| North America | 161 | 0 | 0 | 0.00 | 159 | 1 | 0.6 | 0.43 | | | | |
| Latin America | 420 | 1 | 0.2 | 0.20 | 440 | 0 | 0 | 0.00 | | | | |
| Europe | 471 | 1 | 0.2 | 0.16 | 467 | 1 | 0.2 | 0.16 | | | | |
| Asia | 174 | 0 | 0 | 0.00 | 165 | 0 | 0 | 0.00 | | | | |
| Other | 50 | 0 | 0 | 0.00 | 47 | 0 | 0 | 0.00 | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | |
| Diabetic | 696 | 2 | 0.3 | 0.21 | 698 | 1 | 0.1 | 0.11 | | | | |
| Non-Diabetic | 580 | 0 | 0 | 0.00 | 580 | 1 | 0.2 | 0.13 | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | |
| <30 | 890 | 2 | 0.2 | 0.17 | 836 | 2 | 0.2 | 0.18 | | | | |
| >=30 | 386 | 0 | 0 | 0.00 | 442 | 0 | 0 | 0.00 | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 859 | 2 | 0.2 | 0.18 | 834 | 1 | 0.1 | 0.09 | | | | |
| >=130 | 417 | 0 | 0 | 0.00 | 444 | 1 | 0.2 | 0.16 | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 720 | 2 | 0.3 | 0.21 | 678 | 1 | 0.1 | 0.11 | | | | |
| 75 to <85 | 348 | 0 | 0 | 0.00 | 382 | 1 | 0.3 | 0.19 | | | | |
| >=85 | 208 | 0 | 0 | 0.00 | 218 | 0 | 0 | 0.00 | | | | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.3.1.1.1.3: 1 Cox Regression for time to adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 90 | 0 | 0 | 0.00 | 115 | 1 | 0.9 | 0.65 | | | | |
| 30 to <45 | 349 | 1 | 0.3 | 0.22 | 345 | 0 | 0 | 0.00 | | | | |
| >=45 | 837 | 1 | 0.1 | 0.09 | 818 | 1 | 0.1 | 0.09 | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 452 | 1 | 0.2 | 0.17 | 456 | 1 | 0.2 | 0.16 | | | | |
| Microalbuminuria (30 to <=300) | 628 | 1 | 0.2 | 0.12 | 608 | 0 | 0 | 0.00 | | | | |
| Macroalbuminuria (>300) | 189 | 0 | 0 | 0.00 | 207 | 1 | 0.5 | 0.38 | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | |
| Low, moderate or high | 953 | 1 | 0.1 | 0.08 | 947 | 0 | 0 | 0.00 | | | | |
| Very high | 317 | 1 | 0.3 | 0.24 | 325 | 2 | 0.6 | 0.46 | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | |
| No | 161 | 0 | 0 | 0.00 | 168 | 0 | 0 | 0.00 | | | | |
| Yes | 1115 | 2 | 0.2 | 0.14 | 1110 | 2 | 0.2 | 0.14 | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | | |
| No | 62 | 1 | 1.6 | 1.23 | 72 | 1 | 1.4 | 1.10 | | | | |
| Yes | 1214 | 1 | 0.1 | 0.06 | 1206 | 1 | 0.1 | 0.06 | | | | |
| Baseline use of diuretics | | | | | | | | | | | | |
| No | 46 | 0 | 0 | 0.00 | 57 | 0 | 0 | 0.00 | | | | |
| Yes | 1230 | 2 | 0.2 | 0.12 | 1221 | 2 | 0.2 | 0.12 | | | | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.1.3: 1**

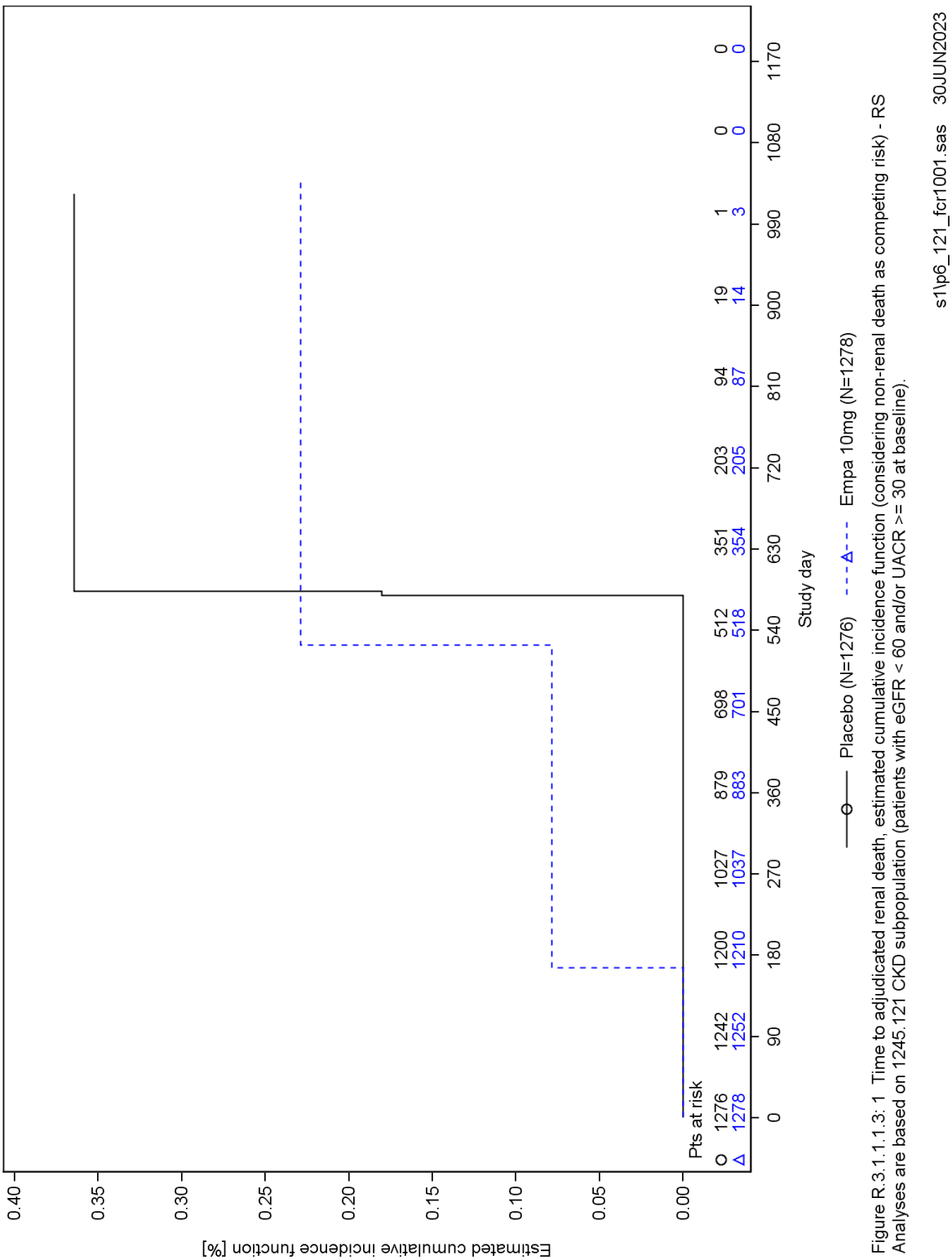


Figure R.3.1.1.1.3: 1 Time to adjudicated renal death, estimated cumulative incidence function (considering non-renal death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.3.1.1.2**

R.3.1.1.2.1 Time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death

Table R.3.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 195 | 15.3 | 14.72 | 1278 | 149 | 11.7 | 10.97 | 0.74 | (0.60,0.91) | 0.0055 | |
| Sex | | | | | | | | | | | | 0.2597 |
| Male | 959 | 144 | 15.0 | 14.18 | 975 | 120 | 12.3 | 11.40 | 0.79 | (0.62,1.01) | 0.0573 | |
| Female | 317 | 51 | 16.1 | 16.47 | 303 | 29 | 9.6 | 9.51 | 0.59 | (0.37,0.93) | 0.0221 | |
| Age [years] | | | | | | | | | | | | 0.4509 |
| <65 | 436 | 69 | 15.8 | 15.58 | 392 | 42 | 10.7 | 10.20 | 0.65 | (0.45,0.96) | 0.0312 | |
| >=65 | 840 | 126 | 15.0 | 14.29 | 886 | 107 | 12.1 | 11.31 | 0.78 | (0.60,1.01) | 0.0634 | |
| Region | | | | | | | | | | | | 0.5072 |
| North America | 161 | 20 | 12.4 | 12.19 | 159 | 24 | 15.1 | 12.60 | 1.04 | (0.57,1.89) | 0.8924 | |
| Latin America | 420 | 70 | 16.7 | 17.48 | 440 | 54 | 12.3 | 12.87 | 0.73 | (0.51,1.04) | 0.0824 | |
| Europe | 471 | 71 | 15.1 | 14.20 | 467 | 50 | 10.7 | 9.85 | 0.69 | (0.48,0.99) | 0.0420 | |
| Asia | 174 | 25 | 14.4 | 11.94 | 165 | 19 | 11.5 | 9.63 | 0.81 | (0.45,1.48) | 0.4998 | |
| Other | 50 | 9 | 18.0 | 17.69 | 47 | 2 | 4.3 | 4.65 | 0.26 | (0.06,1.20) | 0.0851 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9291 |
| Diabetic | 696 | 117 | 16.8 | 16.20 | 698 | 90 | 12.9 | 12.19 | 0.74 | (0.56,0.98) | 0.0350 | |
| Non-Diabetic | 580 | 78 | 13.4 | 12.95 | 580 | 59 | 10.2 | 9.53 | 0.73 | (0.52,1.02) | 0.0679 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9847 |
| <30 | 890 | 141 | 15.8 | 14.82 | 836 | 96 | 11.5 | 10.86 | 0.74 | (0.57,0.96) | 0.0240 | |
| >=30 | 386 | 54 | 14.0 | 14.47 | 442 | 53 | 12.0 | 11.18 | 0.74 | (0.50,1.08) | 0.1173 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.6557 |
| <130 | 859 | 141 | 16.4 | 16.05 | 834 | 100 | 12.0 | 11.51 | 0.72 | (0.56,0.93) | 0.0123 | |
| >=130 | 417 | 54 | 12.9 | 12.11 | 444 | 49 | 11.0 | 10.02 | 0.80 | (0.54,1.18) | 0.2618 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6033 |
| <75 | 720 | 120 | 16.7 | 16.10 | 678 | 86 | 12.7 | 12.24 | 0.77 | (0.58,1.01) | 0.0601 | |
| 75 to <85 | 348 | 49 | 14.1 | 13.36 | 382 | 45 | 11.8 | 10.94 | 0.81 | (0.54,1.22) | 0.3139 | |
| >=85 | 208 | 26 | 12.5 | 12.21 | 218 | 18 | 8.3 | 7.37 | 0.57 | (0.31,1.03) | 0.0639 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

Table R.3.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4314 |
| <30 | 90 | 21 | 23.3 | 26.11 | 115 | 17 | 14.8 | 13.33 | 0.49 | (0.26,0.93) | 0.0286 | |
| 30 to <45 | 349 | 58 | 16.6 | 15.91 | 345 | 44 | 12.8 | 11.95 | 0.76 | (0.51,1.13) | 0.1737 | |
| >=45 | 837 | 116 | 13.9 | 13.18 | 818 | 88 | 10.8 | 10.21 | 0.77 | (0.58,1.01) | 0.0632 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0830 |
| Normal (<30) | 452 | 53 | 11.7 | 11.34 | 456 | 36 | 7.9 | 7.23 | 0.64 | (0.42,0.98) | 0.0393 | |
| Microalbuminuria (30 to <=300) | 628 | 111 | 17.7 | 17.01 | 608 | 72 | 11.8 | 11.27 | 0.66 | (0.49,0.89) | 0.0069 | |
| Macroalbuminuria (>300) | 189 | 29 | 15.3 | 14.45 | 207 | 40 | 19.3 | 18.54 | 1.21 | (0.75,1.96) | 0.4376 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7167 |
| Low, moderate or high | 953 | 133 | 14.0 | 13.41 | 947 | 98 | 10.3 | 9.81 | 0.73 | (0.56,0.94) | 0.0165 | |
| Very high | 317 | 60 | 18.9 | 18.23 | 325 | 51 | 15.7 | 14.35 | 0.79 | (0.54,1.15) | 0.2171 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.8729 |
| No | 161 | 30 | 18.6 | 16.89 | 168 | 23 | 13.7 | 12.53 | 0.71 | (0.41,1.22) | 0.2161 | |
| Yes | 1115 | 165 | 14.8 | 14.38 | 1110 | 126 | 11.4 | 10.73 | 0.74 | (0.59,0.94) | 0.0123 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5829 |
| No | 62 | 12 | 19.4 | 19.10 | 72 | 11 | 15.3 | 16.21 | 0.92 | (0.41,2.09) | 0.8465 | |
| Yes | 1214 | 183 | 15.1 | 14.50 | 1206 | 138 | 11.4 | 10.70 | 0.73 | (0.58,0.91) | 0.0047 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.4831 |
| No | 46 | 4 | 8.7 | 8.13 | 57 | 2 | 3.5 | 3.24 | 0.41 | (0.07,2.22) | 0.2983 | |
| Yes | 1230 | 191 | 15.5 | 14.97 | 1221 | 147 | 12.0 | 11.34 | 0.75 | (0.60,0.93) | 0.0085 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

**Figure R.3.1.1.2.1: 1**

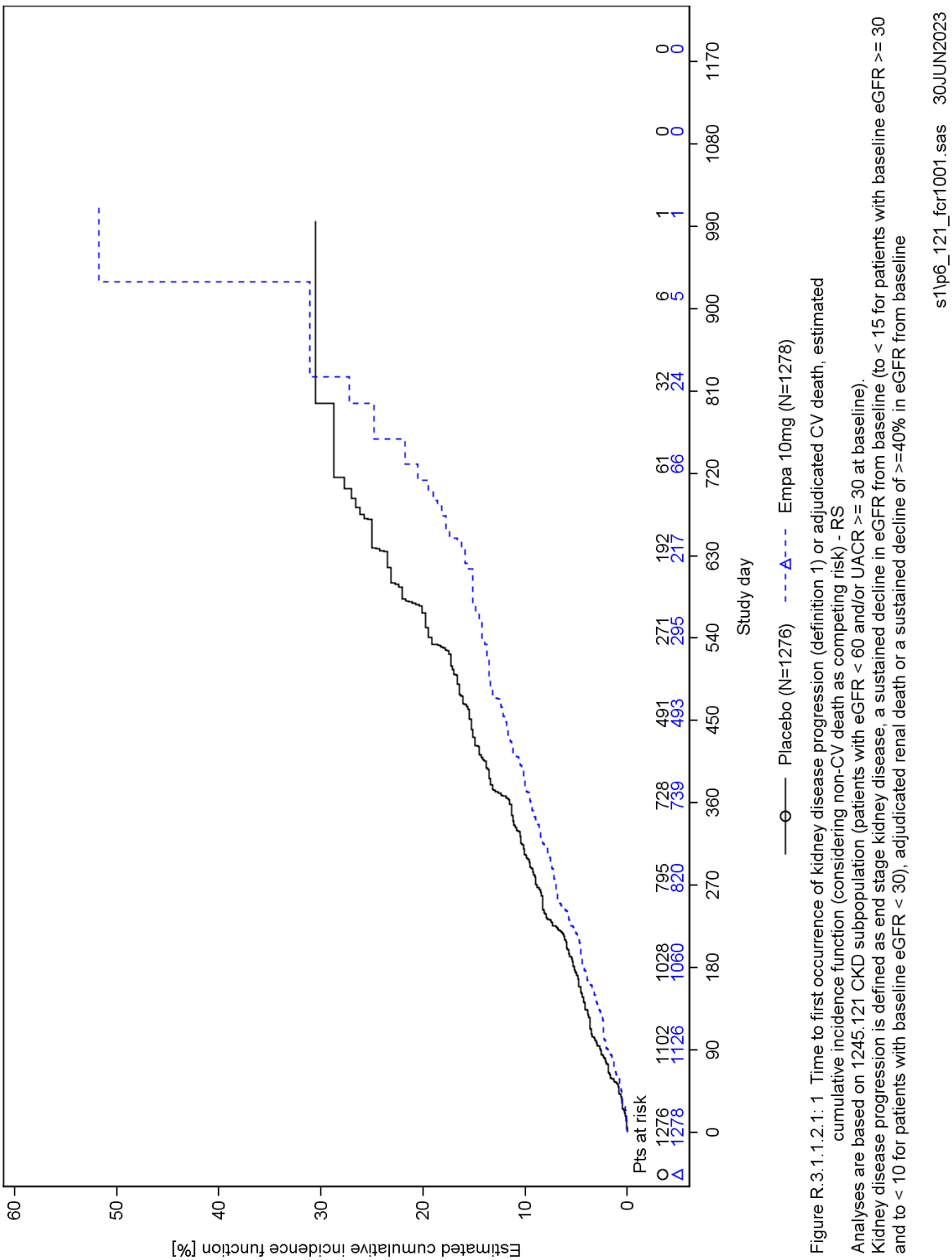


Figure R.3.1.1.2.1: 1 Time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

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R.3.1.1.2.2 Time to first occurrence of kidney disease progression (definition 1)

Table R.3.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 48 | 3.8 | 3.72 | 1278 | 27 | 2.1 | 2.04 | 0.54 | (0.34, 0.86) | 0.0104 | |
| Sex | | | | | | | | | | | | 0.9071 |
| Male | 959 | 36 | 3.8 | 3.64 | 975 | 21 | 2.2 | 2.05 | 0.55 | (0.32, 0.94) | 0.0289 | |
| Female | 317 | 12 | 3.8 | 3.99 | 303 | 6 | 2.0 | 2.02 | 0.51 | (0.19, 1.37) | 0.1824 | |
| Age [years] | | | | | | | | | | | | 0.4435 |
| <65 | 436 | 24 | 5.5 | 5.57 | 392 | 10 | 2.6 | 2.49 | 0.44 | (0.21, 0.92) | 0.0288 | |
| >=65 | 840 | 24 | 2.9 | 2.80 | 886 | 17 | 1.9 | 1.85 | 0.64 | (0.34, 1.19) | 0.1587 | |
| Region | | | | | | | | | | | | 0.0304 |
| North America | 161 | 3 | 1.9 | 1.89 | 159 | 8 | 5.0 | 4.34 | 2.68 | (0.71,10.17) | 0.1469 | |
| Latin America | 420 | 19 | 4.5 | 4.88 | 440 | 14 | 3.2 | 3.42 | 0.69 | (0.35, 1.39) | 0.2994 | |
| Europe | 471 | 20 | 4.2 | 4.11 | 467 | 3 | 0.6 | 0.61 | 0.14 | (0.04, 0.47) | 0.0015 | |
| Asia | 174 | 5 | 2.9 | 2.44 | 165 | 2 | 1.2 | 1.04 | 0.42 | (0.08, 2.19) | 0.3059 | |
| Other | 50 | 1 | 2.0 | 2.02 | 47 | 0 | 0 | 0.00 | <0.01 | | 0.9847 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.8484 |
| Diabetic | 696 | 34 | 4.9 | 4.85 | 698 | 20 | 2.9 | 2.79 | 0.55 | (0.32, 0.96) | 0.0365 | |
| Non-Diabetic | 580 | 14 | 2.4 | 2.38 | 580 | 7 | 1.2 | 1.16 | 0.50 | (0.20, 1.24) | 0.1348 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7974 |
| <30 | 890 | 28 | 3.1 | 3.03 | 836 | 14 | 1.7 | 1.63 | 0.55 | (0.29, 1.04) | 0.0678 | |
| >=30 | 386 | 20 | 5.2 | 5.47 | 442 | 13 | 2.9 | 2.80 | 0.49 | (0.24, 0.98) | 0.0437 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3510 |
| <130 | 859 | 33 | 3.8 | 3.86 | 834 | 14 | 1.7 | 1.66 | 0.44 | (0.24, 0.83) | 0.0110 | |
| >=130 | 417 | 15 | 3.6 | 3.45 | 444 | 13 | 2.9 | 2.70 | 0.71 | (0.33, 1.49) | 0.3602 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3029 |
| <75 | 720 | 28 | 3.9 | 3.87 | 678 | 12 | 1.8 | 1.76 | 0.45 | (0.23, 0.89) | 0.0218 | |
| 75 to <85 | 348 | 11 | 3.2 | 3.07 | 382 | 11 | 2.9 | 2.75 | 0.92 | (0.40, 2.12) | 0.8416 | |
| >=85 | 208 | 9 | 4.3 | 4.34 | 218 | 4 | 1.8 | 1.66 | 0.34 | (0.10, 1.11) | 0.0736 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

Table R.3.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.5124 |
| <30 | 90 | 5 | 5.6 | 6.58 | 115 | 4 | 3.5 | 3.27 | 0.45 | (0.12, 1.69) | 0.2364 | |
| 30 to <45 | 349 | 15 | 4.3 | 4.25 | 345 | 5 | 1.4 | 1.40 | 0.33 | (0.12, 0.91) | 0.0319 | |
| >=45 | 837 | 28 | 3.3 | 3.25 | 818 | 18 | 2.2 | 2.13 | 0.65 | (0.36, 1.17) | 0.1523 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2419 |
| Normal (<30) | 452 | 13 | 2.9 | 2.84 | 456 | 3 | 0.7 | 0.61 | 0.21 | (0.06, 0.74) | 0.0152 | |
| Microalbuminuria (30 to <=300) | 628 | 23 | 3.7 | 3.64 | 608 | 16 | 2.6 | 2.57 | 0.71 | (0.37, 1.34) | 0.2899 | |
| Macroalbuminuria (>300) | 189 | 12 | 6.3 | 6.12 | 207 | 8 | 3.9 | 3.90 | 0.59 | (0.24, 1.45) | 0.2487 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5866 |
| Low, moderate or high | 953 | 32 | 3.4 | 3.30 | 947 | 16 | 1.7 | 1.64 | 0.49 | (0.27, 0.89) | 0.0190 | |
| Very high | 317 | 16 | 5.0 | 5.06 | 325 | 11 | 3.4 | 3.23 | 0.64 | (0.30, 1.38) | 0.2532 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.3481 |
| No | 161 | 5 | 3.1 | 2.90 | 168 | 5 | 3.0 | 2.78 | 0.94 | (0.27, 3.26) | 0.9204 | |
| Yes | 1115 | 43 | 3.9 | 3.85 | 1110 | 22 | 2.0 | 1.92 | 0.49 | (0.29, 0.82) | 0.0069 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4956 |
| No | 62 | 2 | 3.2 | 3.26 | 72 | 2 | 2.8 | 3.05 | 1.05 | (0.15, 7.47) | 0.9623 | |
| Yes | 1214 | 46 | 3.8 | 3.75 | 1206 | 25 | 2.1 | 1.99 | 0.52 | (0.32, 0.85) | 0.0084 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9812 |
| No | 46 | 1 | 2.2 | 2.05 | 57 | 0 | 0 | 0.00 | <0.01 | | 0.9803 | |
| Yes | 1230 | 47 | 3.8 | 3.79 | 1221 | 27 | 2.2 | 2.14 | 0.56 | (0.35, 0.89) | 0.0152 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

**Figure R.3.1.1.2.2: 1**

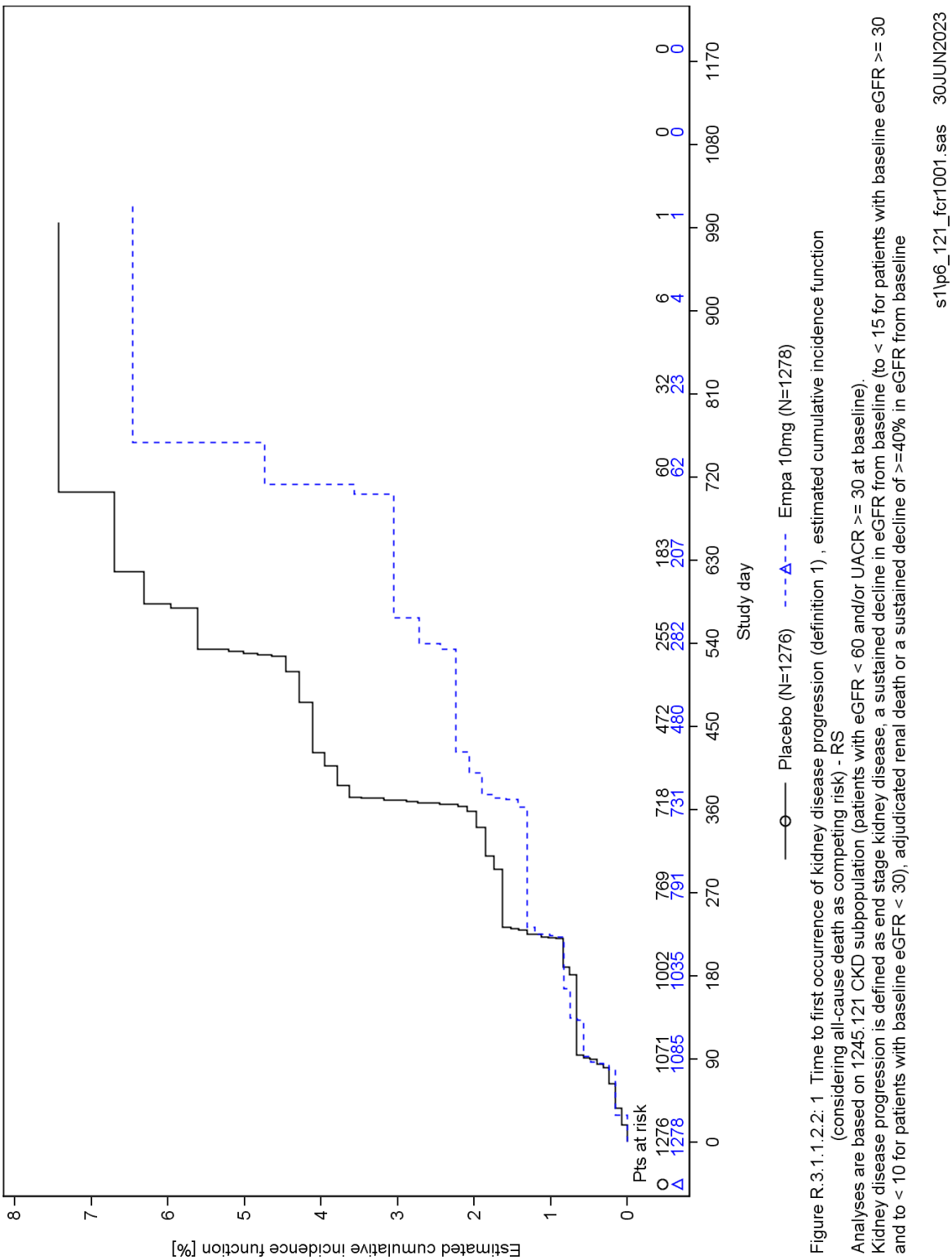


Figure R.3.1.1.2.2: 1 Time to first occurrence of kidney disease progression (definition 1) , estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

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**Figure R.3.1.1.2.2: 2**

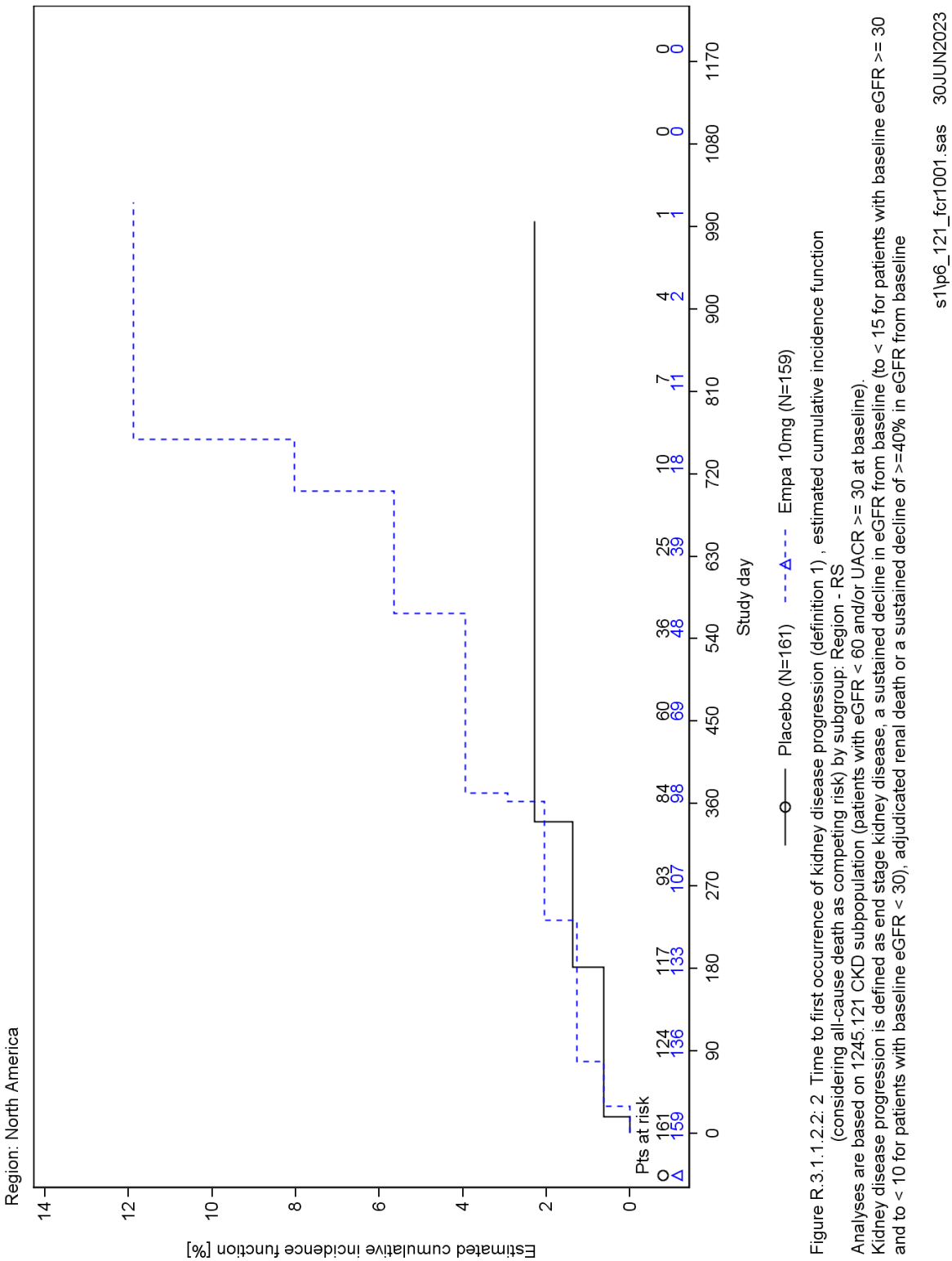


Figure R.3.1.1.2.2: 2 Time to first occurrence of kidney disease progression (definition 1) , estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: Region - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

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**Figure R.3.1.1.2.2: 2**

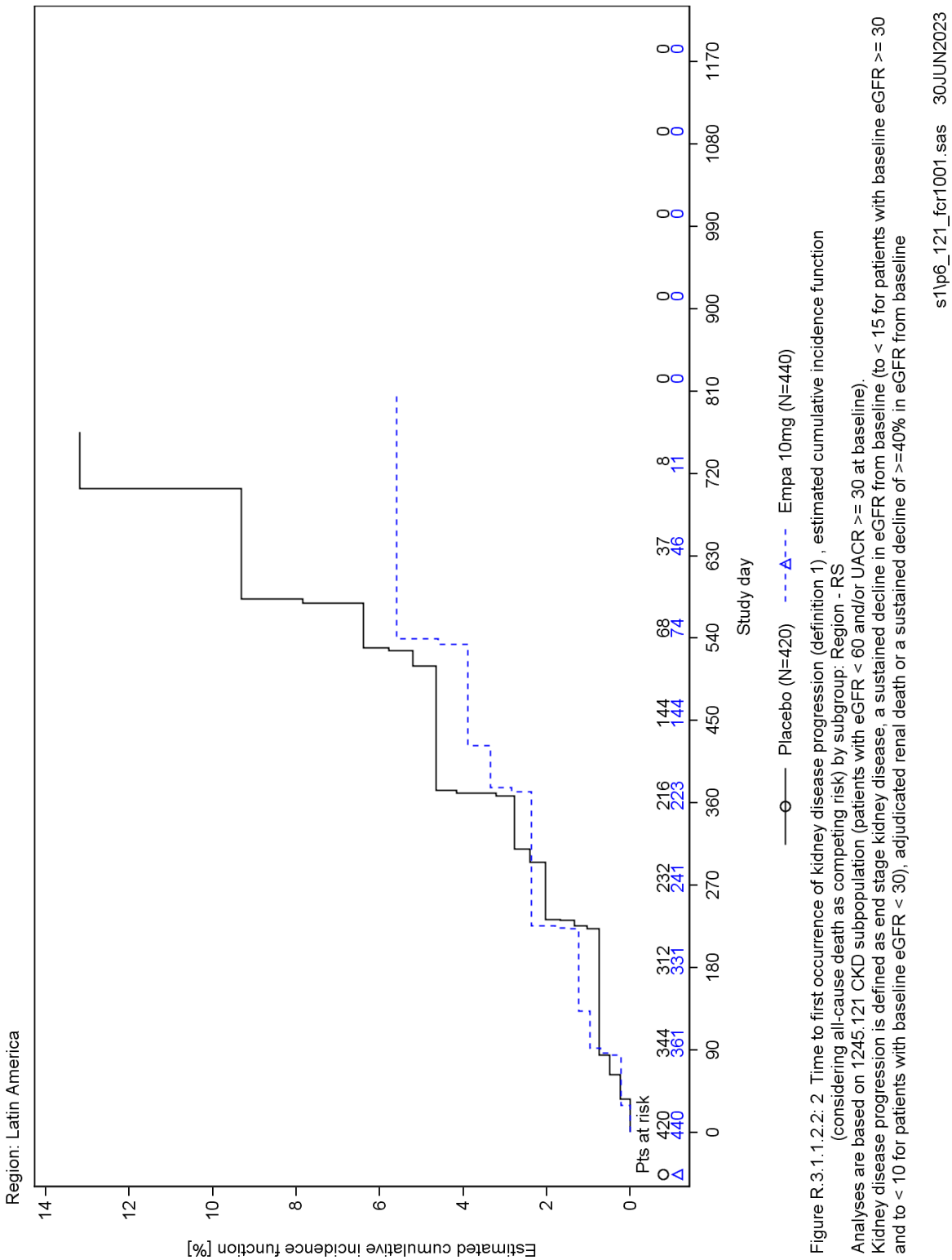


Figure R.3.1.1.2.2: 2 Time to first occurrence of kidney disease progression (definition 1) , estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: Region - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

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**Figure R.3.1.1.2.2: 2**

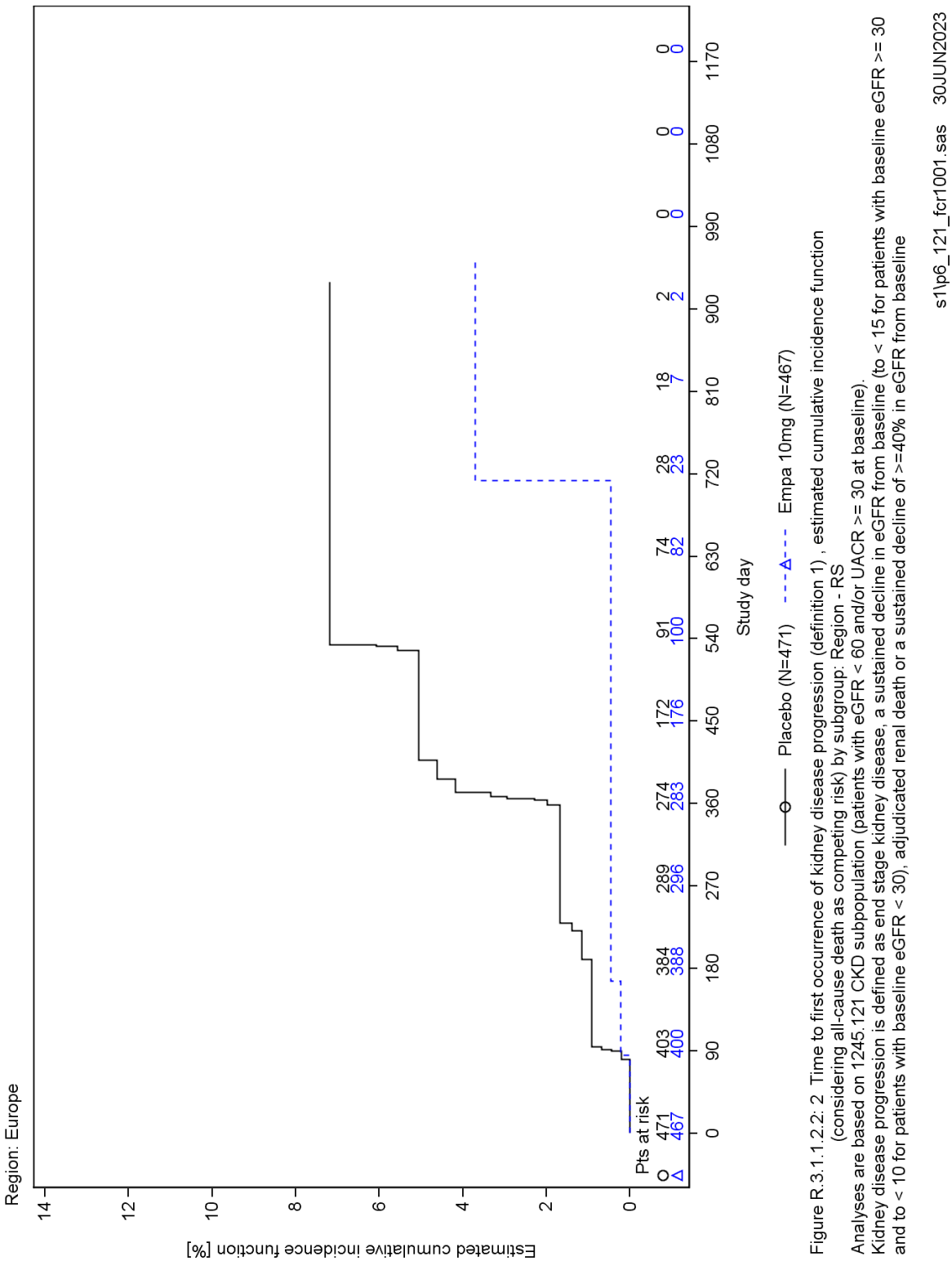


Figure R.3.1.1.2.2: 2 Time to first occurrence of kidney disease progression (definition 1) , estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: Region - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

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**Figure R.3.1.1.2.2: 2**

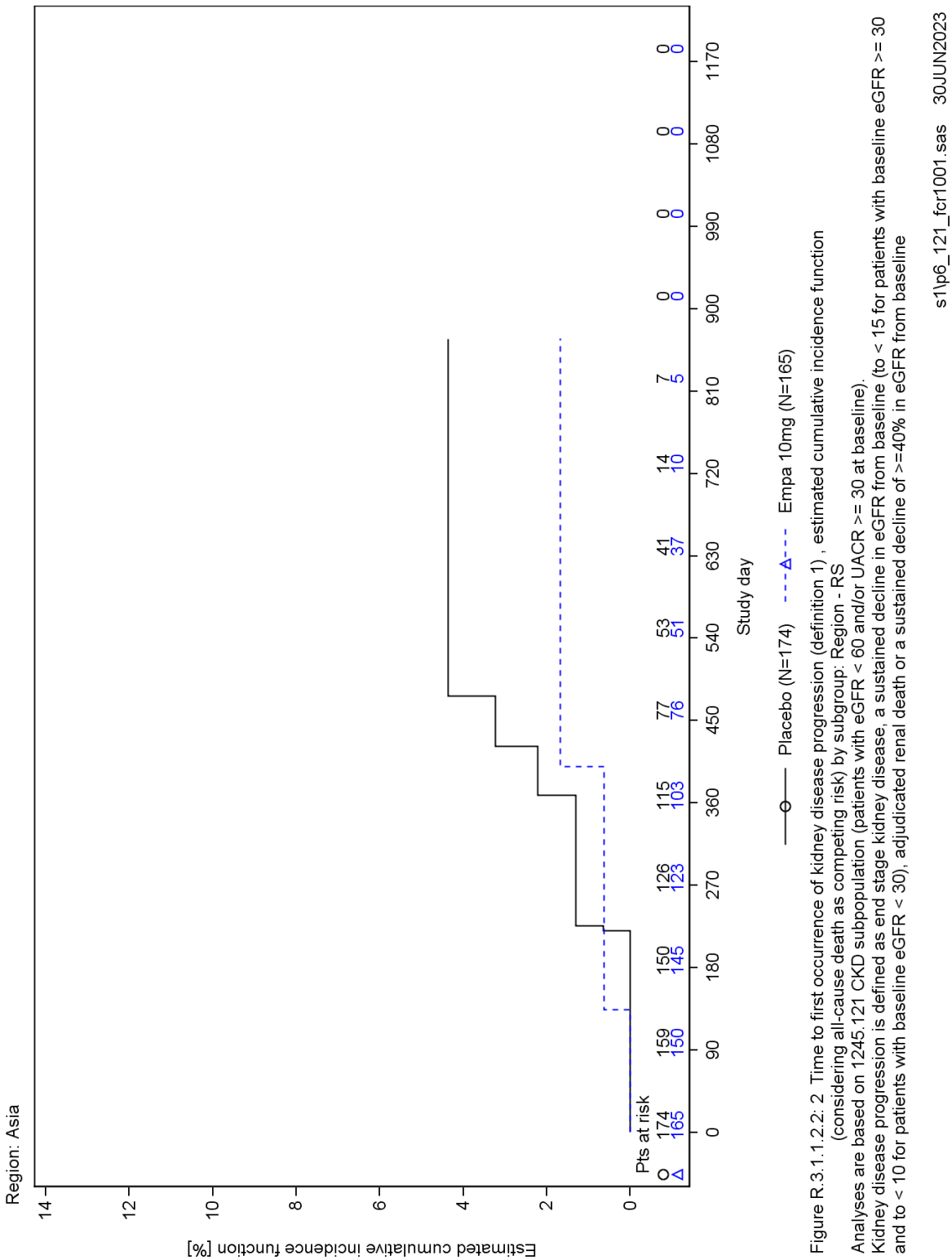


Figure R.3.1.1.2.2: 2 Time to first occurrence of kidney disease progression (definition 1) , estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: Region - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

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**Figure R.3.1.1.2.2: 2**

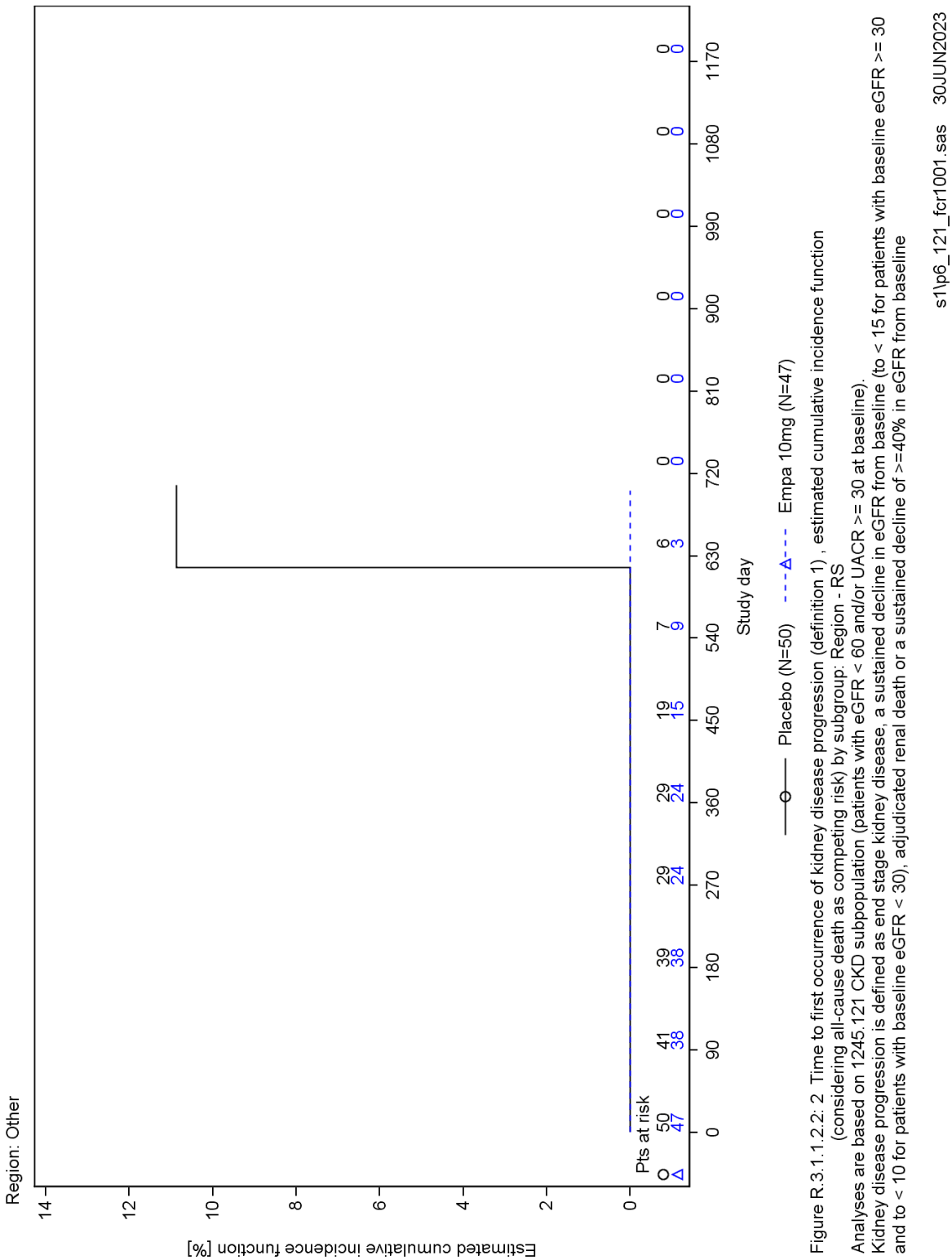


Figure R.3.1.1.2.2: 2 Time to first occurrence of kidney disease progression (definition 1) , estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: Region - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

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R.3.1.1.2.3 Time to first occurrence of kidney disease progression (definition 2)

Table R.3.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 29 | 2.3 | 2.23 | 1278 | 16 | 1.3 | 1.20 | 0.51 | (0.28, 0.94) | 0.0318 | |
| Sex | | | | | | | | | | | | 0.3874 |
| Male | 959 | 22 | 2.3 | 2.21 | 975 | 14 | 1.4 | 1.36 | 0.58 | (0.30, 1.15) | 0.1184 | |
| Female | 317 | 7 | 2.2 | 2.31 | 303 | 2 | 0.7 | 0.66 | 0.27 | (0.06, 1.33) | 0.1077 | |
| Age [years] | | | | | | | | | | | | 0.2417 |
| <65 | 436 | 16 | 3.7 | 3.68 | 392 | 5 | 1.3 | 1.22 | 0.33 | (0.12, 0.91) | 0.0326 | |
| >=65 | 840 | 13 | 1.5 | 1.50 | 886 | 11 | 1.2 | 1.19 | 0.72 | (0.32, 1.61) | 0.4215 | |
| Region | | | | | | | | | | | | 0.1684 |
| North America | 161 | 3 | 1.9 | 1.89 | 159 | 6 | 3.8 | 3.21 | 2.12 | (0.52, 8.60) | 0.2932 | |
| Latin America | 420 | 12 | 2.9 | 3.06 | 440 | 7 | 1.6 | 1.69 | 0.50 | (0.20, 1.29) | 0.1539 | |
| Europe | 471 | 12 | 2.5 | 2.44 | 467 | 2 | 0.4 | 0.41 | 0.15 | (0.03, 0.67) | 0.0133 | |
| Asia | 174 | 2 | 1.1 | 0.96 | 165 | 1 | 0.6 | 0.51 | 0.54 | (0.05, 5.99) | 0.6166 | |
| Other | 50 | 0 | 0 | 0.00 | 47 | 0 | 0 | 0.00 | 0.91 | | 0.9999 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.7226 |
| Diabetic | 696 | 20 | 2.9 | 2.82 | 698 | 12 | 1.7 | 1.65 | 0.54 | (0.26, 1.11) | 0.0951 | |
| Non-Diabetic | 580 | 9 | 1.6 | 1.52 | 580 | 4 | 0.7 | 0.66 | 0.42 | (0.13, 1.37) | 0.1522 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2837 |
| <30 | 890 | 18 | 2.0 | 1.93 | 836 | 11 | 1.3 | 1.28 | 0.66 | (0.31, 1.40) | 0.2752 | |
| >=30 | 386 | 11 | 2.8 | 2.99 | 442 | 5 | 1.1 | 1.06 | 0.32 | (0.11, 0.93) | 0.0370 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3622 |
| <130 | 859 | 24 | 2.8 | 2.78 | 834 | 10 | 1.2 | 1.18 | 0.44 | (0.21, 0.93) | 0.0305 | |
| >=130 | 417 | 5 | 1.2 | 1.14 | 444 | 6 | 1.4 | 1.23 | 0.85 | (0.26, 2.81) | 0.7901 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4500 |
| <75 | 720 | 22 | 3.1 | 3.01 | 678 | 9 | 1.3 | 1.31 | 0.43 | (0.20, 0.94) | 0.0355 | |
| 75 to <85 | 348 | 6 | 1.7 | 1.66 | 382 | 7 | 1.8 | 1.73 | 1.03 | (0.34, 3.08) | 0.9561 | |
| >=85 | 208 | 1 | 0.5 | 0.48 | 218 | 0 | 0 | 0.00 | <0.01 | | 0.9871 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 50% in eGFR from baseline.

Table R.3.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.5924 |
| <30 | 90 | 4 | 4.4 | 5.23 | 115 | 3 | 2.6 | 2.45 | 0.42 | (0.09, 1.90) | 0.2613 | |
| 30 to <45 | 349 | 12 | 3.4 | 3.37 | 345 | 4 | 1.2 | 1.12 | 0.33 | (0.10, 1.02) | 0.0532 | |
| >=45 | 837 | 13 | 1.6 | 1.50 | 818 | 9 | 1.1 | 1.06 | 0.67 | (0.29, 1.58) | 0.3615 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2530 |
| Normal (<30) | 452 | 10 | 2.2 | 2.18 | 456 | 2 | 0.4 | 0.41 | 0.17 | (0.04, 0.78) | 0.0231 | |
| Microalbuminuria (30 to <=300) | 628 | 14 | 2.2 | 2.19 | 608 | 9 | 1.5 | 1.44 | 0.69 | (0.30, 1.61) | 0.3931 | |
| Macroalbuminuria (>300) | 189 | 5 | 2.6 | 2.52 | 207 | 5 | 2.4 | 2.39 | 0.74 | (0.21, 2.58) | 0.6315 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3464 |
| Low, moderate or high | 953 | 17 | 1.8 | 1.74 | 947 | 7 | 0.7 | 0.71 | 0.38 | (0.16, 0.93) | 0.0335 | |
| Very high | 317 | 12 | 3.8 | 3.76 | 325 | 9 | 2.8 | 2.63 | 0.70 | (0.29, 1.66) | 0.4133 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7852 |
| No | 161 | 4 | 2.5 | 2.30 | 168 | 3 | 1.8 | 1.66 | 0.62 | (0.14, 2.80) | 0.5306 | |
| Yes | 1115 | 25 | 2.2 | 2.22 | 1110 | 13 | 1.2 | 1.13 | 0.49 | (0.25, 0.96) | 0.0376 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4791 |
| No | 62 | 1 | 1.6 | 1.60 | 72 | 1 | 1.4 | 1.51 | 1.37 | (0.08,22.24) | 0.8234 | |
| Yes | 1214 | 28 | 2.3 | 2.26 | 1206 | 15 | 1.2 | 1.18 | 0.49 | (0.26, 0.92) | 0.0264 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9900 |
| No | 46 | 1 | 2.2 | 2.05 | 57 | 0 | 0 | 0.00 | <0.01 | | 0.9895 | |
| Yes | 1230 | 28 | 2.3 | 2.24 | 1221 | 16 | 1.3 | 1.26 | 0.53 | (0.29, 0.99) | 0.0471 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 50% in eGFR from baseline.

**Figure R.3.1.1.2.3: 1**

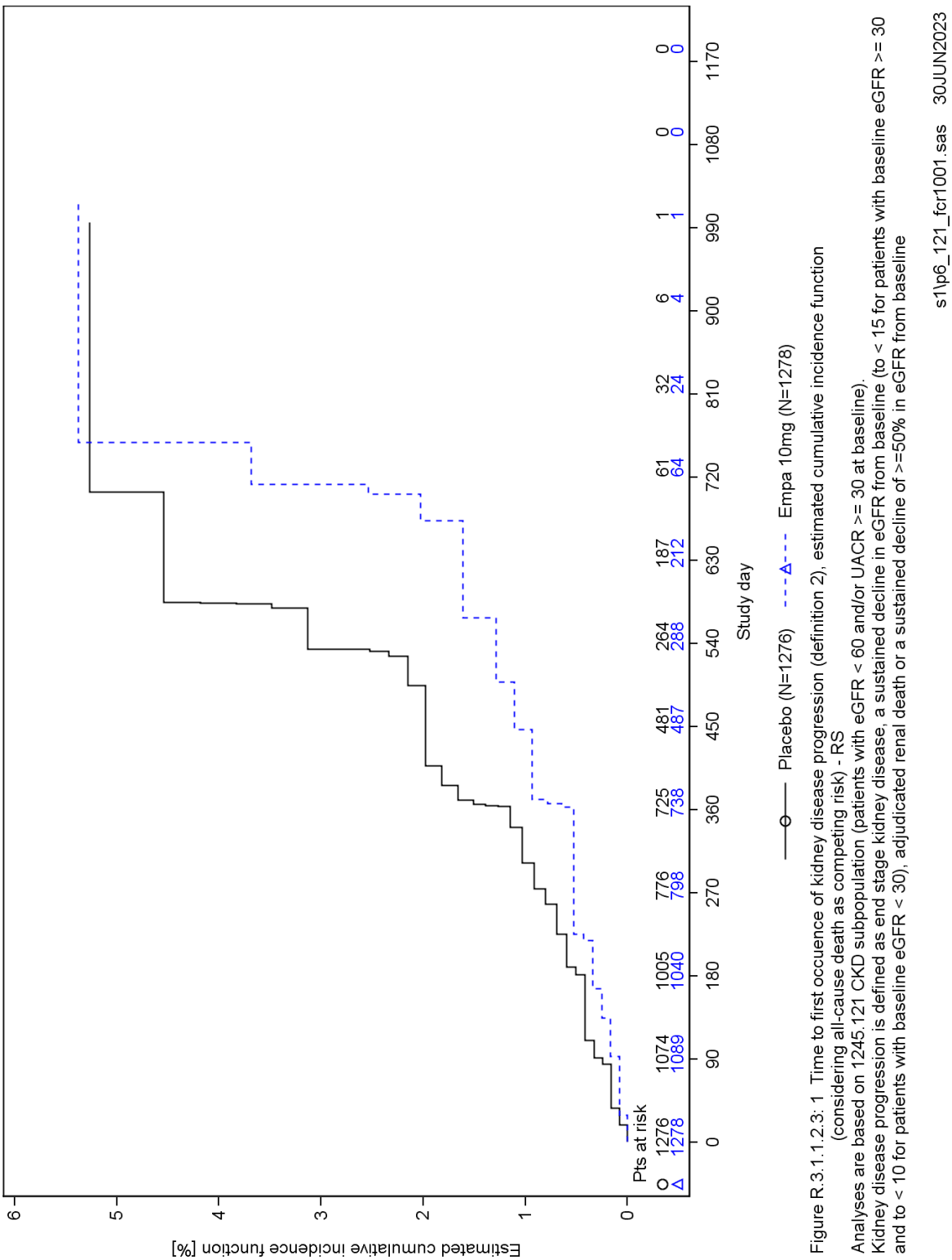


Figure R.3.1.1.2.3: 1 Time to first occuence of kidney disease progression (definition 2), estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=50% in eGFR from baseline

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R.3.1.1.2.4 Time to first occurrence of kidney disease progression (definition 3)

Table R.3.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 18 | 1.4 | 1.38 | 1278 | 11 | 0.9 | 0.82 | 0.56 | (0.26, 1.18) | 0.1281 | |
| Sex | | | | | | | | | | | | 0.3928 |
| Male | 959 | 14 | 1.5 | 1.40 | 975 | 10 | 1.0 | 0.97 | 0.65 | (0.29, 1.47) | 0.2980 | |
| Female | 317 | 4 | 1.3 | 1.32 | 303 | 1 | 0.3 | 0.33 | 0.23 | (0.03, 2.10) | 0.1938 | |
| Age [years] | | | | | | | | | | | | 0.6076 |
| <65 | 436 | 11 | 2.5 | 2.52 | 392 | 5 | 1.3 | 1.22 | 0.48 | (0.16, 1.39) | 0.1739 | |
| >=65 | 840 | 7 | 0.8 | 0.81 | 886 | 6 | 0.7 | 0.65 | 0.71 | (0.24, 2.12) | 0.5400 | |
| Region | | | | | | | | | | | | 0.5260 |
| North America | 161 | 3 | 1.9 | 1.89 | 159 | 4 | 2.5 | 2.14 | 1.55 | (0.34, 7.09) | 0.5709 | |
| Latin America | 420 | 7 | 1.7 | 1.78 | 440 | 5 | 1.1 | 1.20 | 0.60 | (0.19, 1.91) | 0.3845 | |
| Europe | 471 | 8 | 1.7 | 1.63 | 467 | 2 | 0.4 | 0.41 | 0.21 | (0.05, 1.01) | 0.0513 | |
| Asia | 174 | 0 | 0 | 0.00 | 165 | 0 | 0 | 0.00 | 1.03 | | 1.0000 | |
| Other | 50 | 0 | 0 | 0.00 | 47 | 0 | 0 | 0.00 | 0.95 | | 1.0000 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.7543 |
| Diabetic | 696 | 12 | 1.7 | 1.69 | 698 | 8 | 1.1 | 1.10 | 0.60 | (0.24, 1.48) | 0.2705 | |
| Non-Diabetic | 580 | 6 | 1.0 | 1.01 | 580 | 3 | 0.5 | 0.49 | 0.46 | (0.12, 1.86) | 0.2767 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.3213 |
| <30 | 890 | 10 | 1.1 | 1.07 | 836 | 7 | 0.8 | 0.81 | 0.75 | (0.28, 1.99) | 0.5656 | |
| >=30 | 386 | 8 | 2.1 | 2.17 | 442 | 4 | 0.9 | 0.85 | 0.34 | (0.10, 1.15) | 0.0829 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.2674 |
| <130 | 859 | 15 | 1.7 | 1.74 | 834 | 6 | 0.7 | 0.71 | 0.42 | (0.16, 1.09) | 0.0749 | |
| >=130 | 417 | 3 | 0.7 | 0.68 | 444 | 5 | 1.1 | 1.02 | 1.12 | (0.26, 4.77) | 0.8745 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6267 |
| <75 | 720 | 12 | 1.7 | 1.64 | 678 | 5 | 0.7 | 0.73 | 0.45 | (0.16, 1.29) | 0.1357 | |
| 75 to <85 | 348 | 5 | 1.4 | 1.39 | 382 | 6 | 1.6 | 1.49 | 0.99 | (0.30, 3.28) | 0.9847 | |
| >=85 | 208 | 1 | 0.5 | 0.48 | 218 | 0 | 0 | 0.00 | <0.01 | | 0.9927 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 57% in eGFR from baseline.

Table R.3.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8041 |
| <30 | 90 | 3 | 3.3 | 3.93 | 115 | 3 | 2.6 | 2.44 | 0.52 | (0.10, 2.61) | 0.4272 | |
| 30 to <45 | 349 | 8 | 2.3 | 2.23 | 345 | 3 | 0.9 | 0.84 | 0.37 | (0.10, 1.41) | 0.1457 | |
| >=45 | 837 | 7 | 0.8 | 0.81 | 818 | 5 | 0.6 | 0.59 | 0.67 | (0.21, 2.13) | 0.5016 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2595 |
| Normal (<30) | 452 | 8 | 1.8 | 1.74 | 456 | 2 | 0.4 | 0.41 | 0.20 | (0.04, 0.94) | 0.0421 | |
| Microalbuminuria (30 to <=300) | 628 | 7 | 1.1 | 1.09 | 608 | 6 | 1.0 | 0.95 | 0.97 | (0.32, 2.94) | 0.9609 | |
| Macroalbuminuria (>300) | 189 | 3 | 1.6 | 1.50 | 207 | 3 | 1.4 | 1.43 | 0.71 | (0.14, 3.62) | 0.6819 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0397 |
| Low, moderate or high | 953 | 12 | 1.3 | 1.23 | 947 | 3 | 0.3 | 0.30 | 0.22 | (0.06, 0.79) | 0.0205 | |
| Very high | 317 | 6 | 1.9 | 1.87 | 325 | 8 | 2.5 | 2.33 | 1.27 | (0.44, 3.71) | 0.6577 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.4742 |
| No | 161 | 3 | 1.9 | 1.72 | 168 | 1 | 0.6 | 0.55 | 0.26 | (0.03, 2.53) | 0.2433 | |
| Yes | 1115 | 15 | 1.3 | 1.33 | 1110 | 10 | 0.9 | 0.87 | 0.62 | (0.28, 1.39) | 0.2463 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4461 |
| No | 62 | 1 | 1.6 | 1.60 | 72 | 1 | 1.4 | 1.51 | 1.64 | (0.10,27.07) | 0.7297 | |
| Yes | 1214 | 17 | 1.4 | 1.37 | 1206 | 10 | 0.8 | 0.79 | 0.53 | (0.24, 1.16) | 0.1115 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9964 |
| No | 46 | 1 | 2.2 | 2.05 | 57 | 0 | 0 | 0.00 | <0.01 | | 0.9963 | |
| Yes | 1230 | 17 | 1.4 | 1.36 | 1221 | 11 | 0.9 | 0.86 | 0.60 | (0.28, 1.29) | 0.1877 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 57% in eGFR from baseline.

**Figure R.3.1.1.2.4: 1**

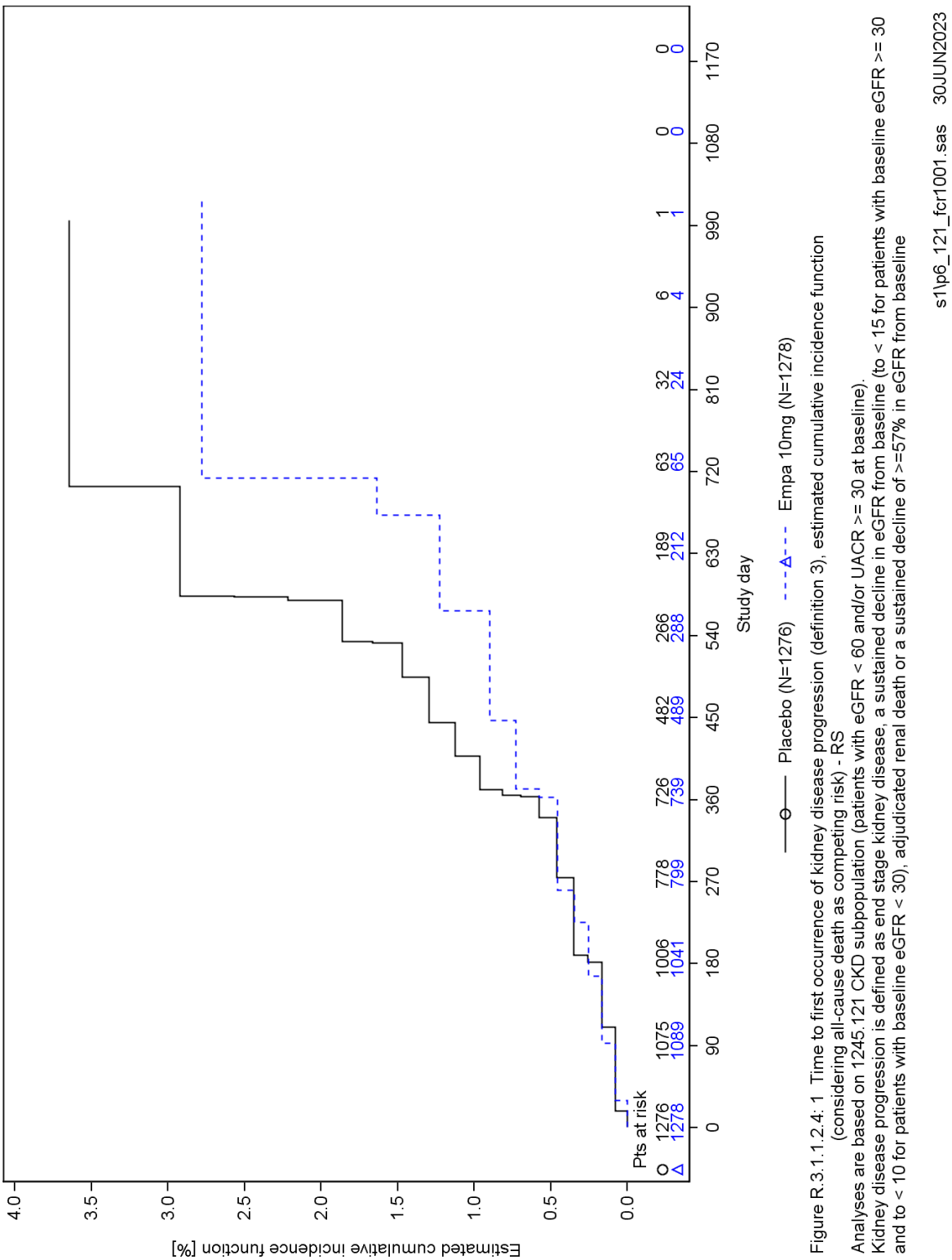


Figure R.3.1.1.2.4: 1 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=57% in eGFR from baseline

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**Figure R.3.1.1.2.4: 2**

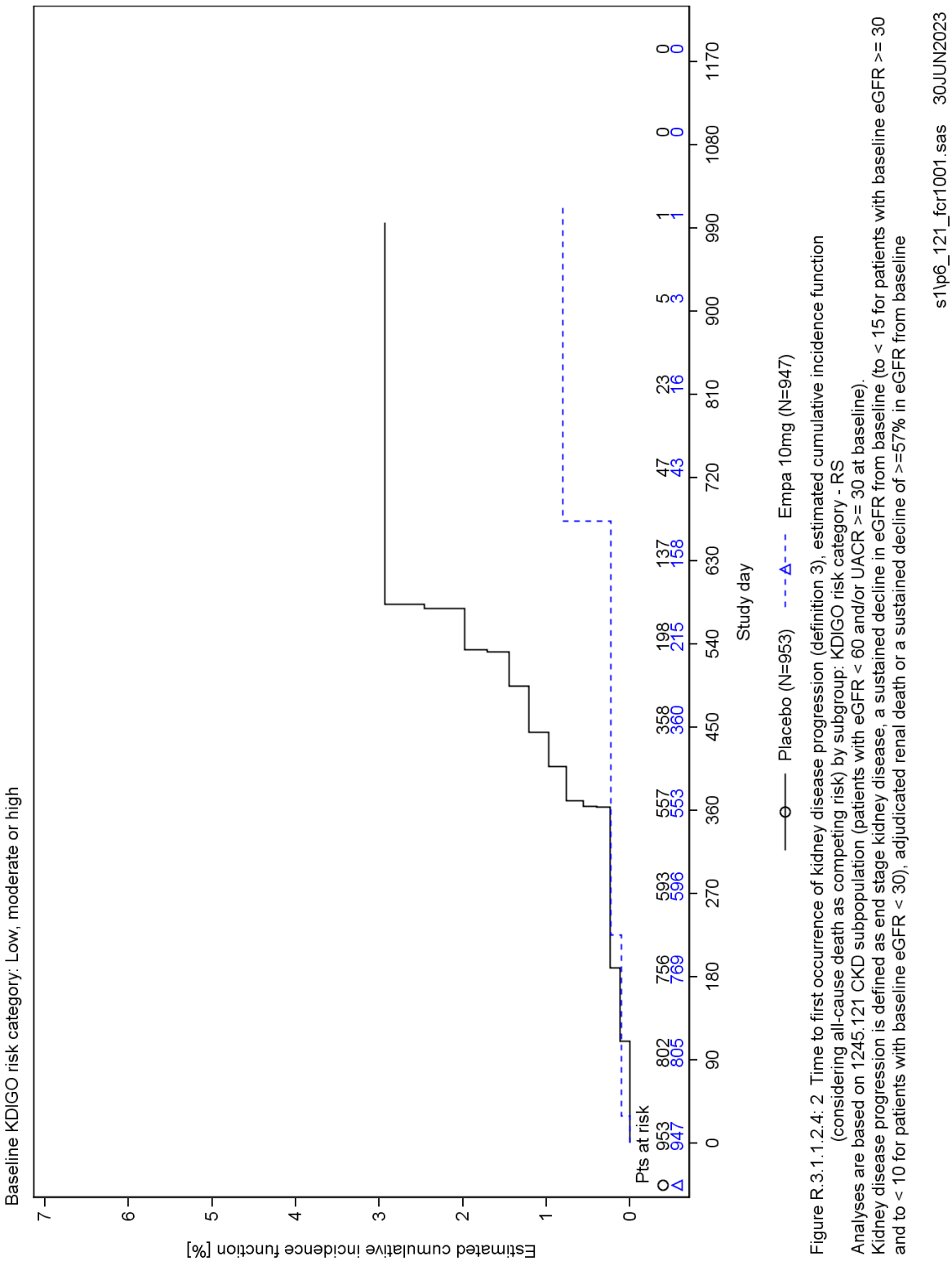


Figure R.3.1.1.2.4: 2 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: KDIGO risk category - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=57% in eGFR from baseline

**Figure R.3.1.1.2.4: 2**

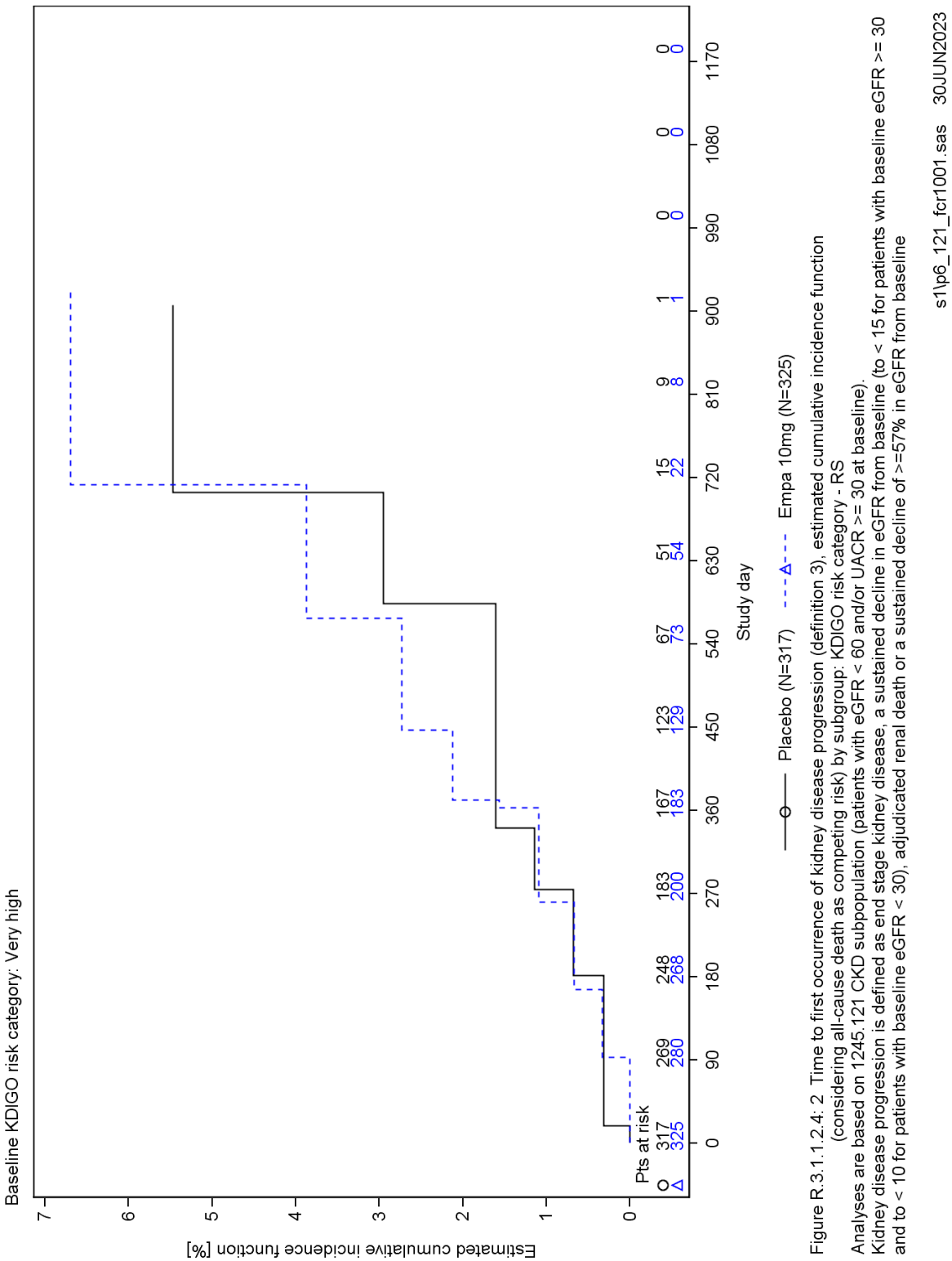


Figure R.3.1.1.2.4: 2 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: KDIGO risk category - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=57% in eGFR from baseline

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R.3.1.1.2.5 Time to first occurrence of sustained decline of >= 40% in eGFR

Table R.3.1.1.2.5: 1 Cox Regression for time to first occurrence of sustained decline of >= 40% in eGFR until the end of planned treatment period overall - RS

| Subgroup Category | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 39 | 3.1 | 3.03 | 1278 | 23 | 1.8 | 1.74 | 0.57 | (0.34,0.96) | 0.0332 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.2.5: 1**

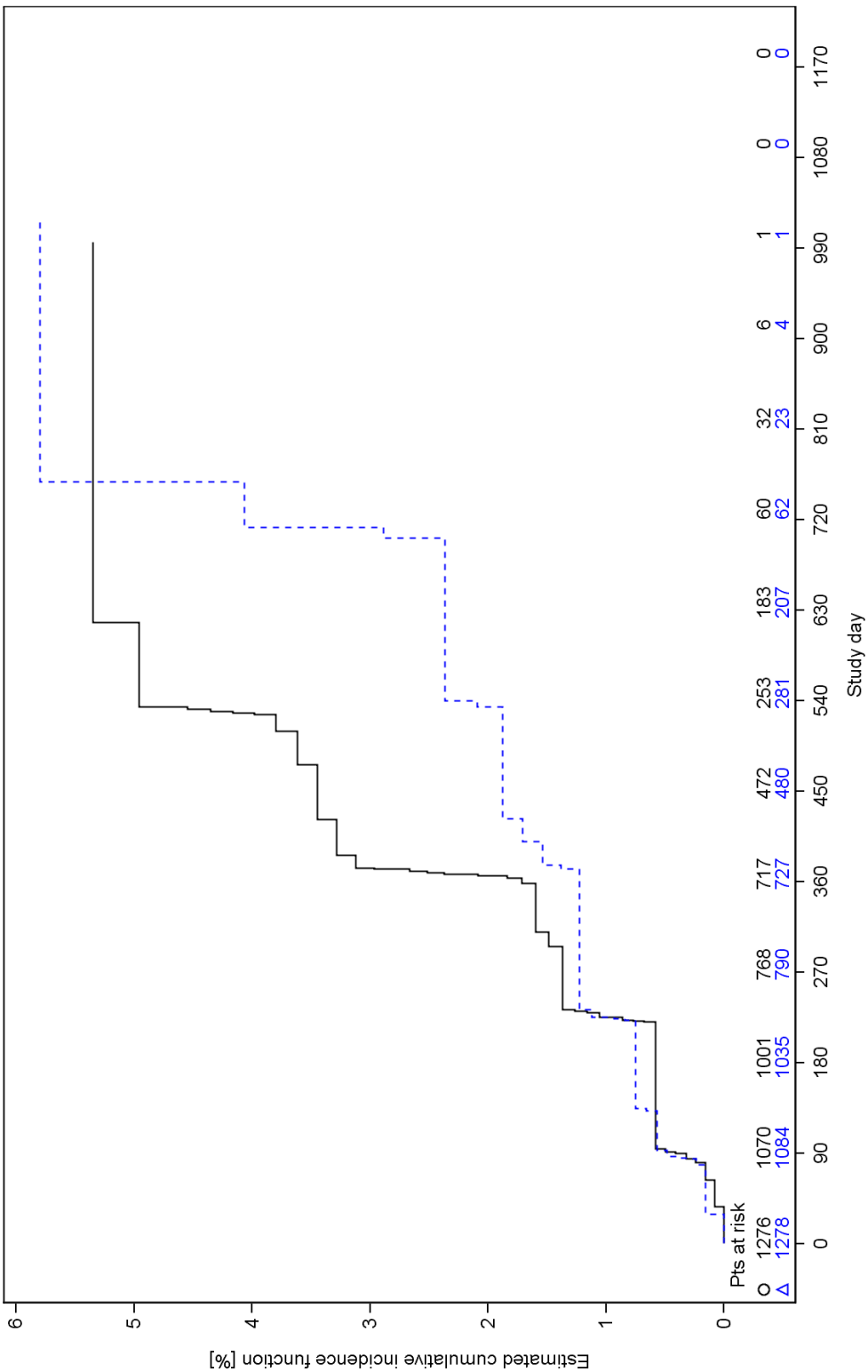


Figure R.3.1.1.2.5: 1 Time to first occurrence of sustained decline of >= 40% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.3.1.1.2.6 Time to first occurrence of sustained decline of >= 50% in eGFR

Table R.3.1.1.2.6: 1 Cox Regression for time to first occurrence of sustained decline of >= 50% in eGFR until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1276 | 19 | 1.5 | 1.46 | 1278 | 11 | 0.9 | 0.83 | 0.53 | (0.25,1.13) | 0.1010 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.2.6: 1**

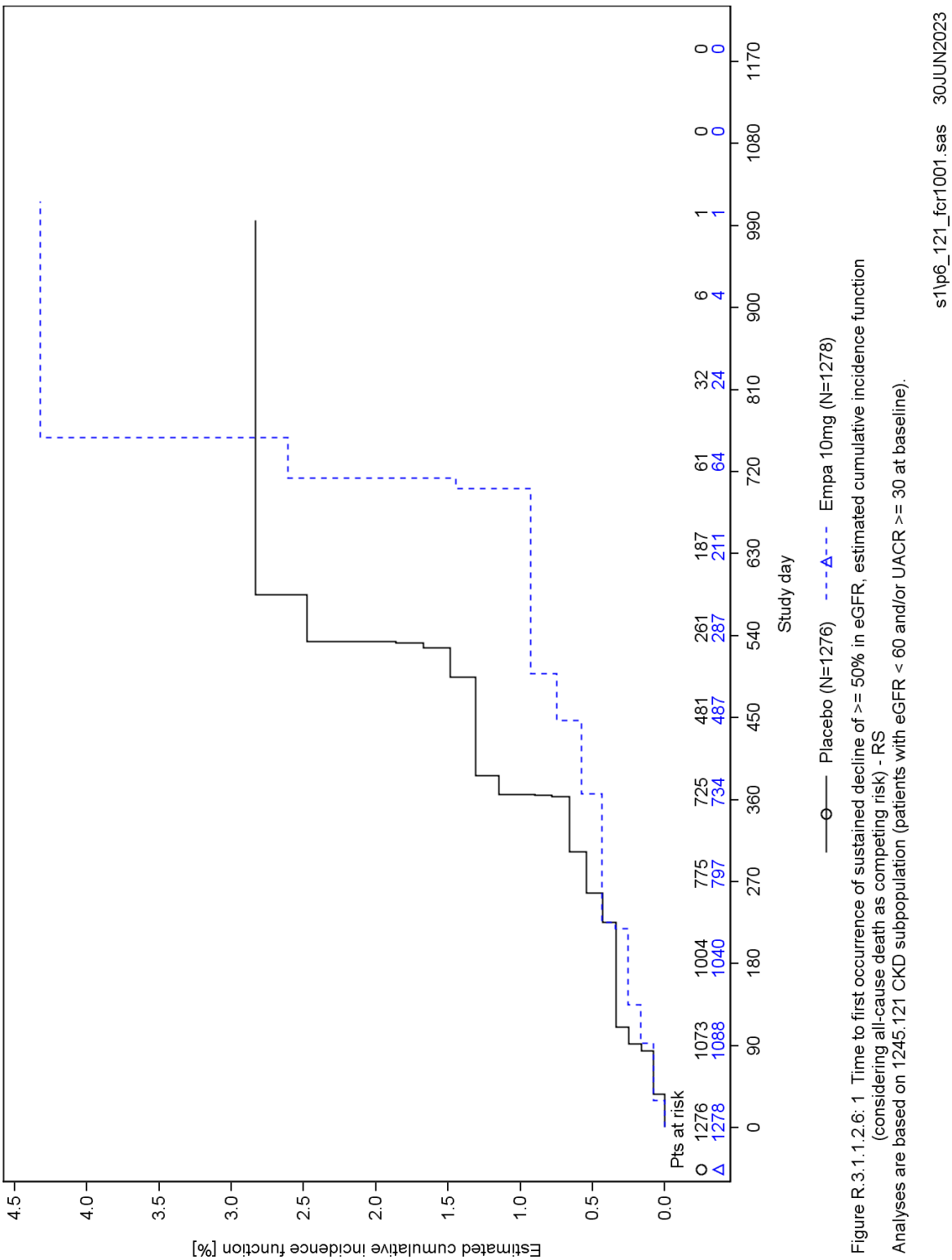


Figure R.3.1.1.2.6: 1 Time to first occurrence of sustained decline of >= 50% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.3.1.1.2.7 Time to first occurrence of sustained decline of >= 57% in eGFR

Table R.3.1.1.2.7: 1 Cox Regression for time to first occurrence of sustained decline of >= 57% in eGFR until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1276 | 8 | 0.6 | 0.61 | 1278 | 6 | 0.5 | 0.45 | 0.63 | (0.22,1.84) | 0.4001 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.2.7: 1**

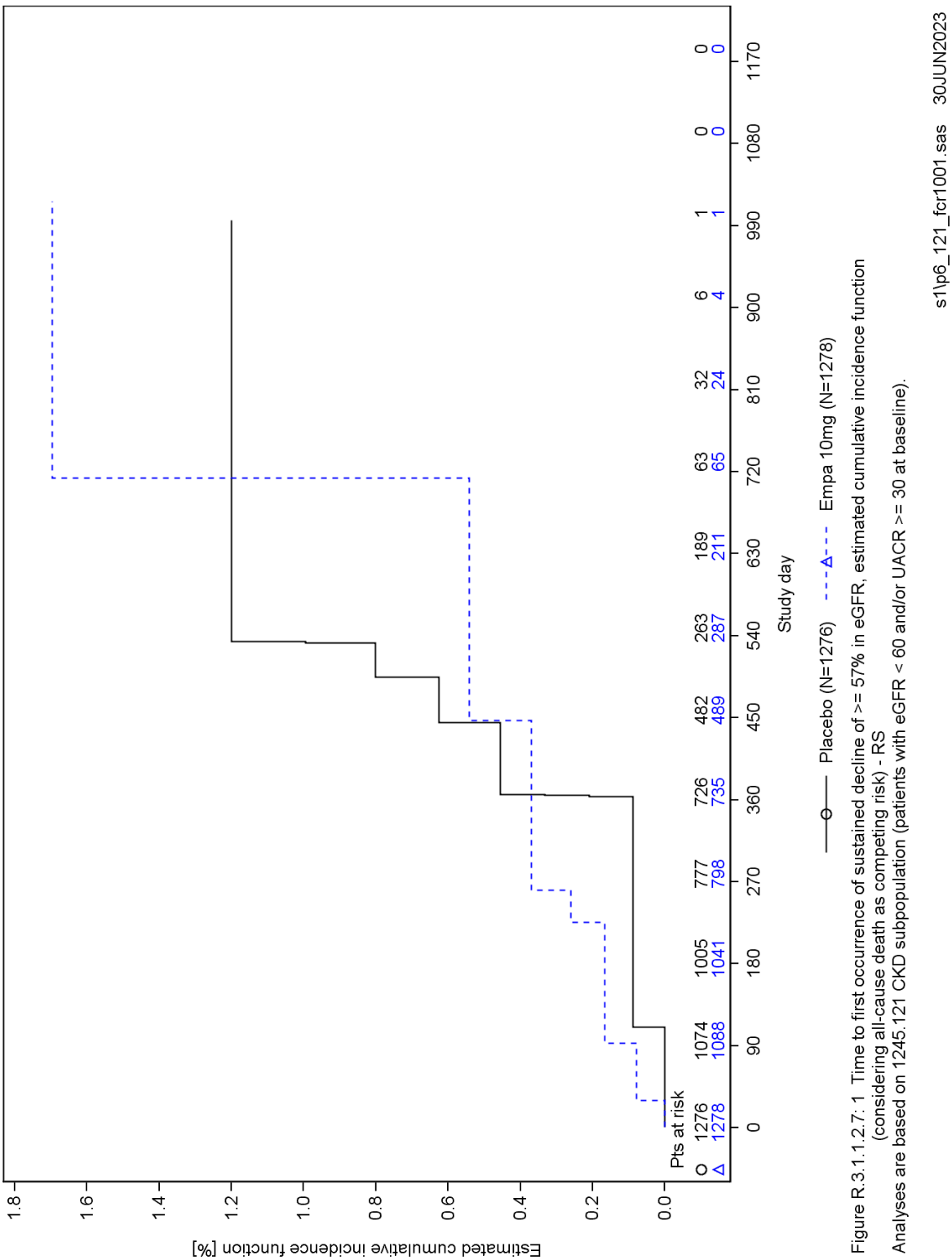


Figure R.3.1.1.2.7: 1 Time to first occurrence of sustained decline of >= 57% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.3.1.1.2.8**

R.3.1.1.2.8 Time to ESKD

Table R.3.1.1.2.8: 1 Cox Regression for time to ESKD until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1276 | 9 | 0.7 | 0.54 | 1278 | 4 | 0.3 | 0.24 | 0.46 | (0.14,1.52) | 0.2037 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

**Figure R.3.1.1.2.8: 1**

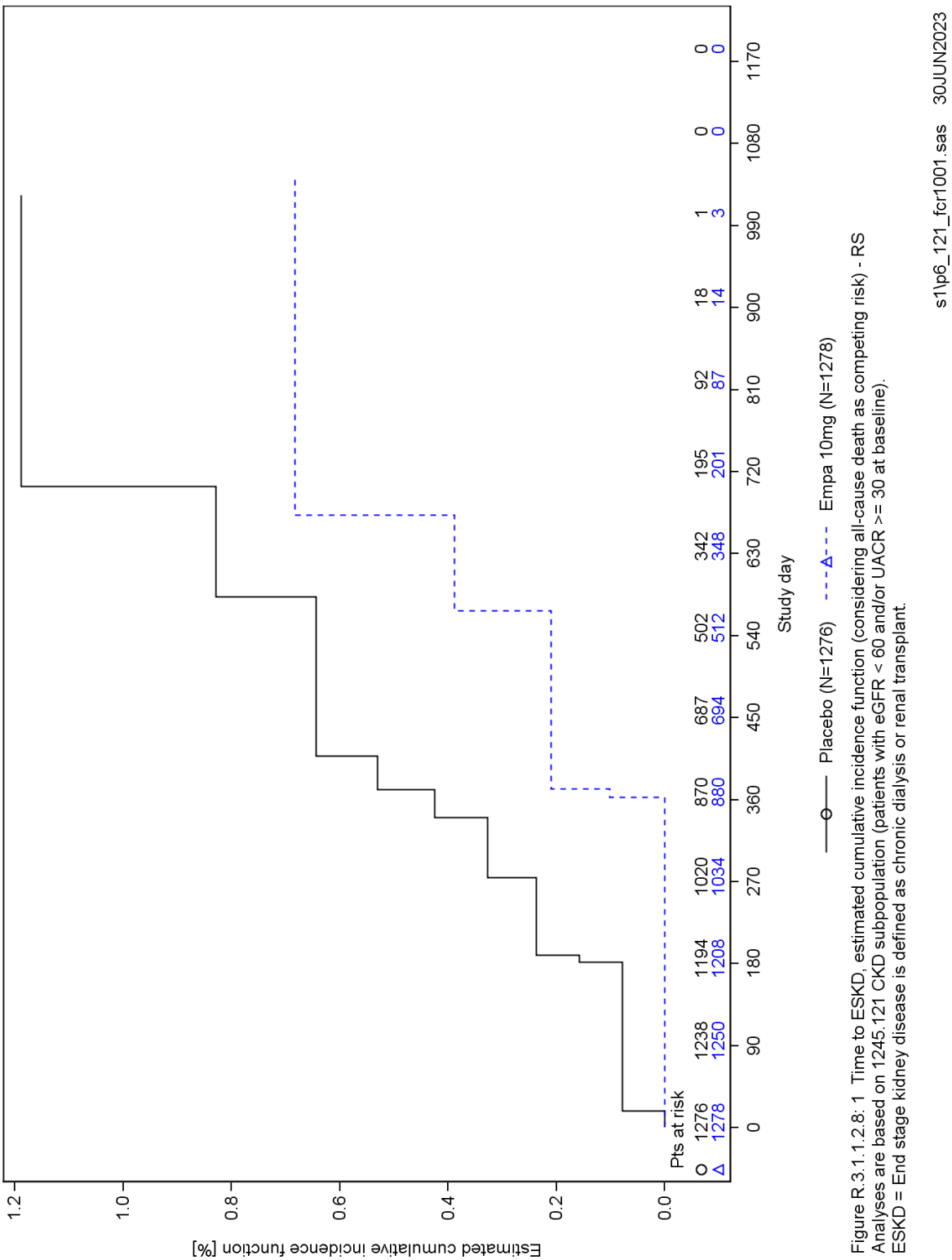


Figure R.3.1.1.2.8: 1 Time to ESKD, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

R.3.1.1.2.9 Time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death

Table R.3.1.1.2.9: 1 Cox Regression for time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 14 | 1.1 | 1.07 | 1278 | 7 | 0.5 | 0.52 | 0.43 | (0.17, 1.06) | 0.0674 | |
| Sex | | | | | | | | | | | | 0.4347 |
| Male | 959 | 10 | 1.0 | 1.00 | 975 | 6 | 0.6 | 0.58 | 0.52 | (0.19, 1.45) | 0.2137 | |
| Female | 317 | 4 | 1.3 | 1.32 | 303 | 1 | 0.3 | 0.33 | 0.20 | (0.02, 1.80) | 0.1503 | |
| Age [years] | | | | | | | | | | | | 0.3149 |
| <65 | 436 | 8 | 1.8 | 1.83 | 392 | 2 | 0.5 | 0.49 | 0.24 | (0.05, 1.16) | 0.0754 | |
| >=65 | 840 | 6 | 0.7 | 0.69 | 886 | 5 | 0.6 | 0.54 | 0.66 | (0.20, 2.17) | 0.4937 | |
| Region | | | | | | | | | | | | |
| North America | 161 | 3 | 1.9 | 1.89 | 159 | 3 | 1.9 | 1.60 | | | | |
| Latin America | 420 | 5 | 1.2 | 1.27 | 440 | 2 | 0.5 | 0.48 | | | | |
| Europe | 471 | 6 | 1.3 | 1.22 | 467 | 2 | 0.4 | 0.41 | | | | |
| Asia | 174 | 0 | 0 | 0.00 | 165 | 0 | 0 | 0.00 | | | | |
| Other | 50 | 0 | 0 | 0.00 | 47 | 0 | 0 | 0.00 | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2814 |
| Diabetic | 696 | 11 | 1.6 | 1.55 | 698 | 4 | 0.6 | 0.55 | 0.30 | (0.09, 0.96) | 0.0420 | |
| Non-Diabetic | 580 | 3 | 0.5 | 0.51 | 580 | 3 | 0.5 | 0.49 | 0.89 | (0.18, 4.44) | 0.8898 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2255 |
| <30 | 890 | 8 | 0.9 | 0.86 | 836 | 5 | 0.6 | 0.58 | 0.67 | (0.22, 2.06) | 0.4820 | |
| >=30 | 386 | 6 | 1.6 | 1.62 | 442 | 2 | 0.5 | 0.42 | 0.20 | (0.04, 0.99) | 0.0491 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1475 |
| <130 | 859 | 12 | 1.4 | 1.39 | 834 | 3 | 0.4 | 0.35 | 0.25 | (0.07, 0.90) | 0.0333 | |
| >=130 | 417 | 2 | 0.5 | 0.45 | 444 | 4 | 0.9 | 0.82 | 1.22 | (0.22, 6.85) | 0.8173 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6242 |
| <75 | 720 | 10 | 1.4 | 1.36 | 678 | 3 | 0.4 | 0.44 | 0.33 | (0.09, 1.20) | 0.0912 | |
| 75 to <85 | 348 | 3 | 0.9 | 0.83 | 382 | 4 | 1.0 | 0.99 | 0.88 | (0.19, 4.08) | 0.8754 | |
| >=85 | 208 | 1 | 0.5 | 0.48 | 218 | 0 | 0 | 0.00 | <0.01 | | 0.9937 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

Table R.3.1.1.2.9: 1 Cox Regression for time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 90 | 3 | 3.3 | 3.93 | 115 | 3 | 2.6 | 2.44 | | | | |
| 30 to <45 | 349 | 7 | 2.0 | 1.95 | 345 | 2 | 0.6 | 0.56 | | | | |
| >=45 | 837 | 4 | 0.5 | 0.46 | 818 | 2 | 0.2 | 0.23 | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 452 | 7 | 1.5 | 1.52 | 456 | 2 | 0.4 | 0.41 | | | | |
| Microalbuminuria (30 to <=300) | 628 | 5 | 0.8 | 0.78 | 608 | 3 | 0.5 | 0.48 | | | | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 1.00 | 207 | 2 | 1.0 | 0.95 | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0851 |
| Low, moderate or high | 953 | 8 | 0.8 | 0.82 | 947 | 1 | 0.1 | 0.10 | 0.11 | (0.01, 0.89) | 0.0383 | |
| Very high | 317 | 6 | 1.9 | 1.87 | 325 | 6 | 1.8 | 1.75 | 0.89 | (0.28, 2.81) | 0.8493 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5480 |
| No | 161 | 3 | 1.9 | 1.72 | 168 | 1 | 0.6 | 0.55 | 0.22 | (0.02, 2.26) | 0.2031 | |
| Yes | 1115 | 11 | 1.0 | 0.97 | 1110 | 6 | 0.5 | 0.52 | 0.48 | (0.18, 1.31) | 0.1523 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.1763 |
| No | 62 | 1 | 1.6 | 1.60 | 72 | 1 | 1.4 | 1.51 | 3.06 | (0.18,52.63) | 0.4410 | |
| Yes | 1214 | 13 | 1.1 | 1.05 | 1206 | 6 | 0.5 | 0.47 | 0.38 | (0.14, 1.01) | 0.0522 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9969 |
| No | 46 | 1 | 2.2 | 2.05 | 57 | 0 | 0 | 0.00 | <0.01 | | 0.9967 | |
| Yes | 1230 | 13 | 1.1 | 1.04 | 1221 | 7 | 0.6 | 0.55 | 0.46 | (0.18, 1.17) | 0.1034 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.3.1.1.2.9: 1**

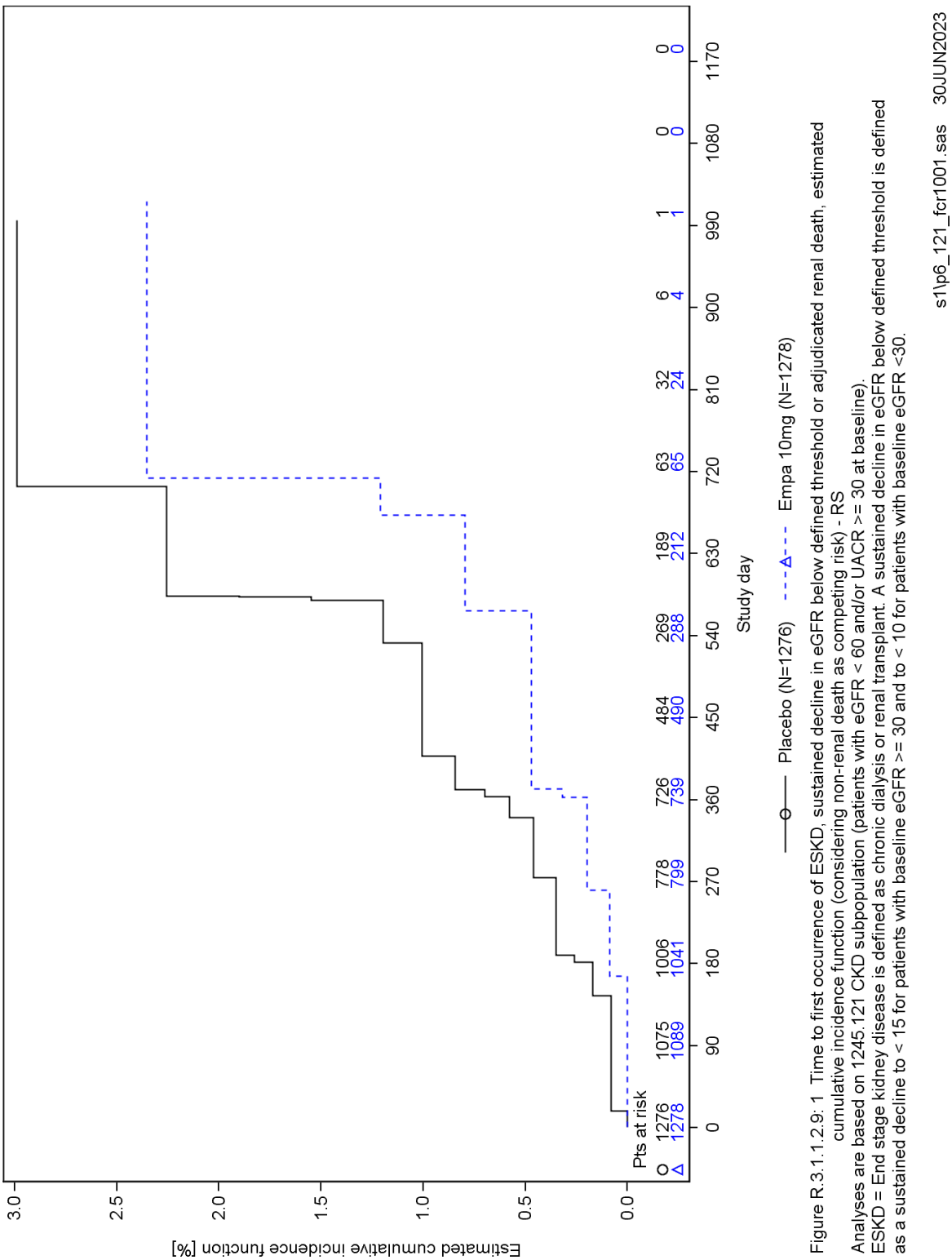


Figure R.3.1.1.2.9: 1 Time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death, estimated cumulative incidence function (considering non-renal death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

R.3.1.1.2.10 Time to first occurrence of ESKD or sustained decline in eGFR below defined threshold

Table R.3.1.1.2.10: 1 Cox Regression for time to first occurrence of ESKD or a sustained decline in eGFR below defined threshold until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 12 | 0.9 | 0.92 | 1278 | 6 | 0.5 | 0.45 | 0.43 | (0.16,1.16) | 0.0968 | |
| Sex | | | | | | | | | | | | 0.3965 |
| Male | 959 | 8 | 0.8 | 0.80 | 975 | 5 | 0.5 | 0.48 | 0.57 | (0.18,1.75) | 0.3227 | |
| Female | 317 | 4 | 1.3 | 1.32 | 303 | 1 | 0.3 | 0.33 | 0.19 | (0.02,1.76) | 0.1448 | |
| Age [years] | | | | | | | | | | | | |
| <65 | 436 | 7 | 1.6 | 1.60 | 392 | 2 | 0.5 | 0.49 | | | | |
| >=65 | 840 | 5 | 0.6 | 0.58 | 886 | 4 | 0.5 | 0.43 | | | | |
| Region | | | | | | | | | | | | |
| North America | 161 | 3 | 1.9 | 1.89 | 159 | 3 | 1.9 | 1.60 | | | | |
| Latin America | 420 | 4 | 1.0 | 1.01 | 440 | 2 | 0.5 | 0.48 | | | | |
| Europe | 471 | 5 | 1.1 | 1.02 | 467 | 1 | 0.2 | 0.20 | | | | |
| Asia | 174 | 0 | 0 | 0.00 | 165 | 0 | 0 | 0.00 | | | | |
| Other | 50 | 0 | 0 | 0.00 | 47 | 0 | 0 | 0.00 | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.6939 |
| Diabetic | 696 | 9 | 1.3 | 1.27 | 698 | 4 | 0.6 | 0.55 | 0.38 | (0.12,1.24) | 0.1096 | |
| Non-Diabetic | 580 | 3 | 0.5 | 0.51 | 580 | 2 | 0.3 | 0.33 | 0.58 | (0.10,3.51) | 0.5560 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2402 |
| <30 | 890 | 6 | 0.7 | 0.64 | 836 | 4 | 0.5 | 0.46 | 0.70 | (0.20,2.52) | 0.5904 | |
| >=30 | 386 | 6 | 1.6 | 1.62 | 442 | 2 | 0.5 | 0.42 | 0.20 | (0.04,1.04) | 0.0552 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1196 |
| <130 | 859 | 10 | 1.2 | 1.16 | 834 | 2 | 0.2 | 0.24 | 0.20 | (0.04,0.93) | 0.0407 | |
| >=130 | 417 | 2 | 0.5 | 0.45 | 444 | 4 | 0.9 | 0.82 | 1.27 | (0.23,7.06) | 0.7887 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.8965 |
| <75 | 720 | 8 | 1.1 | 1.09 | 678 | 3 | 0.4 | 0.44 | 0.40 | (0.11,1.54) | 0.1851 | |
| 75 to <85 | 348 | 3 | 0.9 | 0.83 | 382 | 3 | 0.8 | 0.74 | 0.67 | (0.13,3.43) | 0.6319 | |
| >=85 | 208 | 1 | 0.5 | 0.48 | 218 | 0 | 0 | 0.00 | <0.01 | | 0.9944 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

Table R.3.1.1.2.10: 1 Cox Regression for time to first occurrence of ESKD or a sustained decline in eGFR below defined threshold until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 90 | 3 | 3.3 | 3.93 | 115 | 2 | 1.7 | 1.63 | | | | |
| 30 to <45 | 349 | 6 | 1.7 | 1.67 | 345 | 2 | 0.6 | 0.56 | | | | |
| >=45 | 837 | 3 | 0.4 | 0.35 | 818 | 2 | 0.2 | 0.23 | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 452 | 6 | 1.3 | 1.30 | 456 | 1 | 0.2 | 0.20 | | | | |
| Microalbuminuria (30 to <=300) | 628 | 4 | 0.6 | 0.62 | 608 | 3 | 0.5 | 0.48 | | | | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 1.00 | 207 | 2 | 1.0 | 0.95 | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.1142 |
| Low, moderate or high | 953 | 7 | 0.7 | 0.71 | 947 | 1 | 0.1 | 0.10 | 0.13 | (0.02,1.03) | 0.0537 | |
| Very high | 317 | 5 | 1.6 | 1.56 | 325 | 5 | 1.5 | 1.46 | 0.91 | (0.26,3.20) | 0.8854 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6368 |
| No | 161 | 3 | 1.9 | 1.72 | 168 | 1 | 0.6 | 0.55 | 0.26 | (0.03,2.68) | 0.2589 | |
| Yes | 1115 | 9 | 0.8 | 0.80 | 1110 | 5 | 0.5 | 0.43 | 0.49 | (0.16,1.47) | 0.2014 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9998 |
| No | 62 | 0 | 0 | 0.00 | 72 | 0 | 0 | 0.00 | 2.56 | | 0.9999 | |
| Yes | 1214 | 12 | 1.0 | 0.97 | 1206 | 6 | 0.5 | 0.47 | 0.42 | (0.16,1.13) | 0.0869 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9969 |
| No | 46 | 1 | 2.2 | 2.05 | 57 | 0 | 0 | 0.00 | <0.01 | | 0.9968 | |
| Yes | 1230 | 11 | 0.9 | 0.88 | 1221 | 6 | 0.5 | 0.47 | 0.48 | (0.18,1.31) | 0.1504 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.3.1.1.2.10: 1**

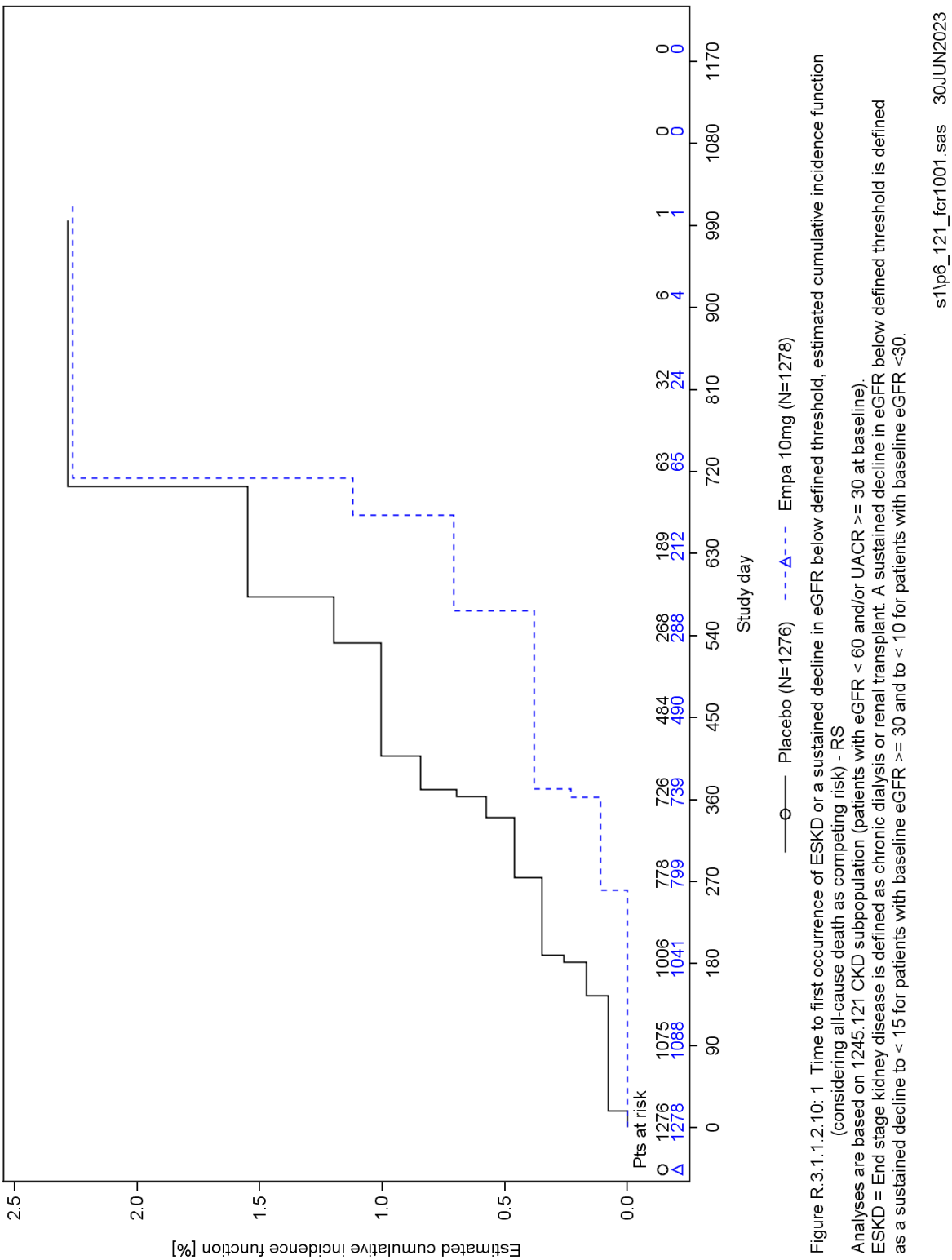


Figure R.3.1.1.2.10: 1 Time to first occurrence of ESKD or a sustained decline in eGFR below defined threshold, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

R.3.1.1.2.11 Time to first occurrence of sustained decline in eGFR below defined threshold

Table R.3.1.1.2.11: 1 Cox Regression for time to first occurrence of a sustained decline in eGFR below defined threshold until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1276 | 4 | 0.3 | 0.31 | 1278 | 2 | 0.2 | 0.15 | 0.32 | (0.05,1.88) | 0.2052 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.3.1.1.2.11: 1**

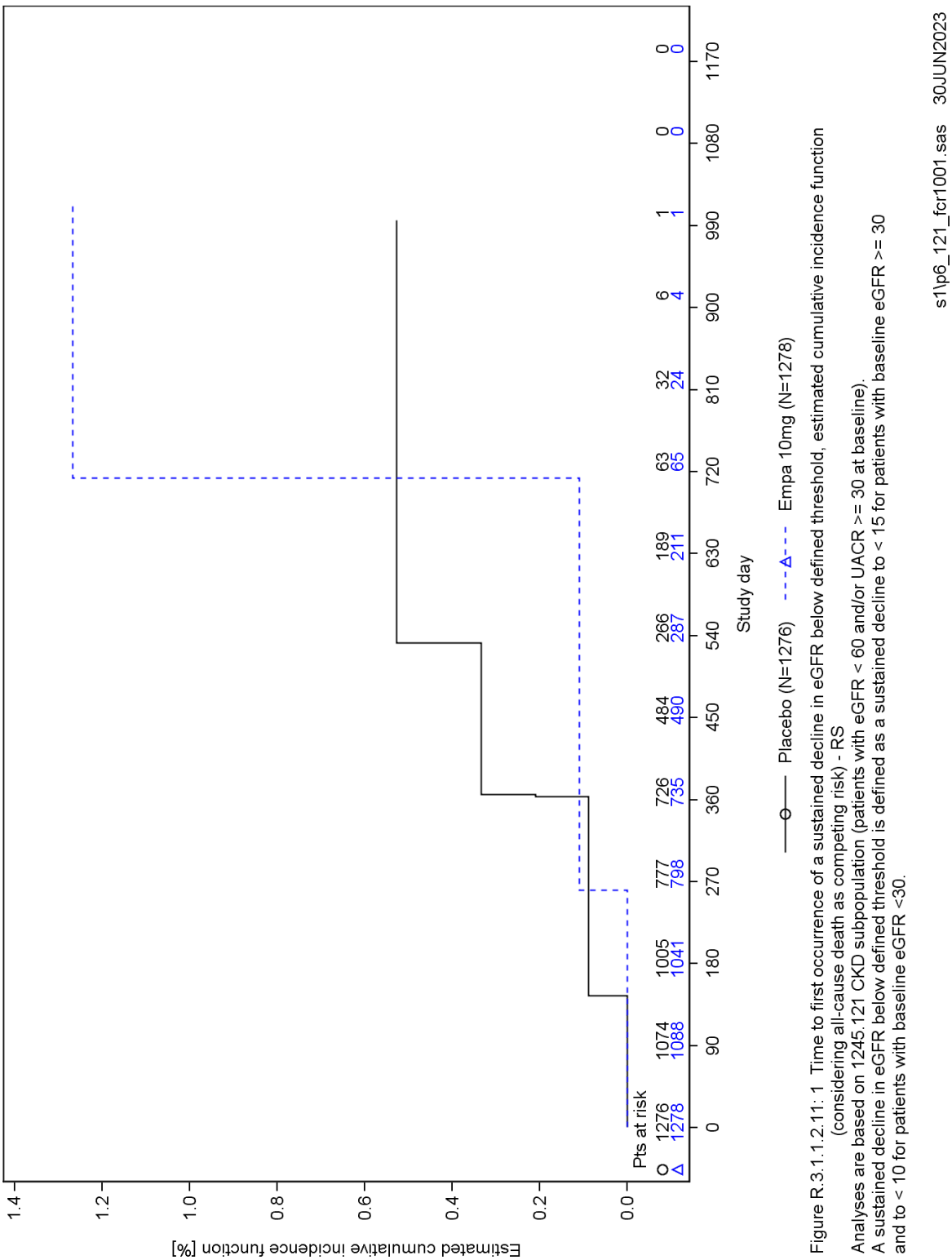


Figure R.3.1.1.2.11: 1 Time to first occurrence of a sustained decline in eGFR below defined threshold, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

R.3.1.1.2.12 Time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2

Table R.3.1.1.2.12: 1 Cox Regression for time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2 until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 13 | 1.0 | 1.00 | 1278 | 6 | 0.5 | 0.45 | 0.40 | (0.15,1.06) | 0.0646 | |
| Sex | | | | | | | | | | | | 0.4615 |
| Male | 959 | 9 | 0.9 | 0.90 | 975 | 5 | 0.5 | 0.48 | 0.50 | (0.16,1.50) | 0.2147 | |
| Female | 317 | 4 | 1.3 | 1.32 | 303 | 1 | 0.3 | 0.33 | 0.20 | (0.02,1.79) | 0.1487 | |
| Age [years] | | | | | | | | | | | | 0.5419 |
| <65 | 436 | 7 | 1.6 | 1.60 | 392 | 2 | 0.5 | 0.49 | 0.28 | (0.06,1.40) | 0.1219 | |
| >=65 | 840 | 6 | 0.7 | 0.69 | 886 | 4 | 0.5 | 0.43 | 0.54 | (0.15,1.91) | 0.3349 | |
| Region | | | | | | | | | | | | |
| North America | 161 | 3 | 1.9 | 1.89 | 159 | 3 | 1.9 | 1.60 | | | | |
| Latin America | 420 | 4 | 1.0 | 1.01 | 440 | 2 | 0.5 | 0.48 | | | | |
| Europe | 471 | 6 | 1.3 | 1.22 | 467 | 1 | 0.2 | 0.20 | | | | |
| Asia | 174 | 0 | 0 | 0.00 | 165 | 0 | 0 | 0.00 | | | | |
| Other | 50 | 0 | 0 | 0.00 | 47 | 0 | 0 | 0.00 | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.6115 |
| Diabetic | 696 | 10 | 1.4 | 1.41 | 698 | 4 | 0.6 | 0.55 | 0.34 | (0.10,1.09) | 0.0699 | |
| Non-Diabetic | 580 | 3 | 0.5 | 0.51 | 580 | 2 | 0.3 | 0.33 | 0.59 | (0.10,3.55) | 0.5641 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1773 |
| <30 | 890 | 6 | 0.7 | 0.64 | 836 | 4 | 0.5 | 0.46 | 0.71 | (0.20,2.53) | 0.5929 | |
| >=30 | 386 | 7 | 1.8 | 1.90 | 442 | 2 | 0.5 | 0.42 | 0.17 | (0.04,0.85) | 0.0311 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0927 |
| <130 | 859 | 11 | 1.3 | 1.27 | 834 | 2 | 0.2 | 0.24 | 0.18 | (0.04,0.83) | 0.0273 | |
| >=130 | 417 | 2 | 0.5 | 0.45 | 444 | 4 | 0.9 | 0.82 | 1.30 | (0.23,7.25) | 0.7643 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.8525 |
| <75 | 720 | 9 | 1.3 | 1.23 | 678 | 3 | 0.4 | 0.44 | 0.36 | (0.10,1.34) | 0.1266 | |
| 75 to <85 | 348 | 3 | 0.9 | 0.83 | 382 | 3 | 0.8 | 0.74 | 0.66 | (0.13,3.36) | 0.6144 | |
| >=85 | 208 | 1 | 0.5 | 0.48 | 218 | 0 | 0 | 0.00 | <0.01 | | 0.9944 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

Table R.3.1.1.2.12: 1 Cox Regression for time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2 until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 90 | 4 | 4.4 | 5.23 | 115 | 2 | 1.7 | 1.63 | | | | |
| 30 to <45 | 349 | 6 | 1.7 | 1.67 | 345 | 2 | 0.6 | 0.56 | | | | |
| >=45 | 837 | 3 | 0.4 | 0.35 | 818 | 2 | 0.2 | 0.23 | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 452 | 6 | 1.3 | 1.30 | 456 | 1 | 0.2 | 0.20 | | | | |
| Microalbuminuria (30 to <=300) | 628 | 5 | 0.8 | 0.78 | 608 | 3 | 0.5 | 0.48 | | | | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 1.00 | 207 | 2 | 1.0 | 0.95 | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.1488 |
| Low, moderate or high | 953 | 7 | 0.7 | 0.71 | 947 | 1 | 0.1 | 0.10 | 0.13 | (0.02,1.04) | 0.0546 | |
| Very high | 317 | 6 | 1.9 | 1.87 | 325 | 5 | 1.5 | 1.46 | 0.76 | (0.23,2.53) | 0.6548 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6538 |
| No | 161 | 3 | 1.9 | 1.72 | 168 | 1 | 0.6 | 0.55 | 0.25 | (0.02,2.50) | 0.2357 | |
| Yes | 1115 | 10 | 0.9 | 0.89 | 1110 | 5 | 0.5 | 0.43 | 0.44 | (0.15,1.30) | 0.1385 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9998 |
| No | 62 | 0 | 0 | 0.00 | 72 | 0 | 0 | 0.00 | 2.71 | | 0.9999 | |
| Yes | 1214 | 13 | 1.1 | 1.05 | 1206 | 6 | 0.5 | 0.47 | 0.39 | (0.15,1.03) | 0.0566 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9970 |
| No | 46 | 1 | 2.2 | 2.05 | 57 | 0 | 0 | 0.00 | <0.01 | | 0.9969 | |
| Yes | 1230 | 12 | 1.0 | 0.96 | 1221 | 6 | 0.5 | 0.47 | 0.44 | (0.16,1.17) | 0.1004 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

**Figure R.3.1.1.2.12: 1**

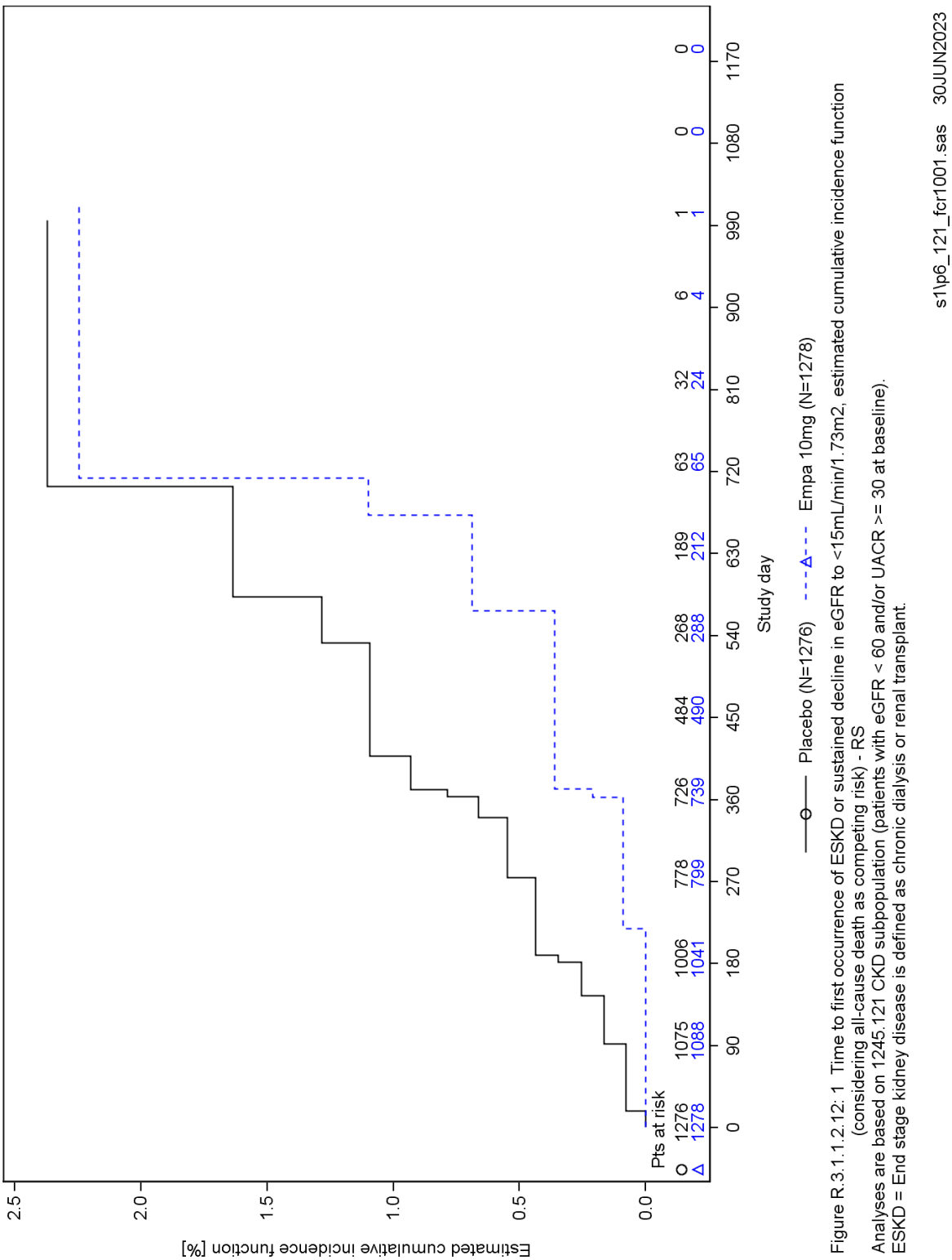


Figure R.3.1.1.2.12: 1 Time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

R.3.1.1.2.13 Time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2

Table R.3.1.1.2.13: 1 Cox Regression for time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2 until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1276 | 5 | 0.4 | 0.38 | 1278 | 2 | 0.2 | 0.15 | 0.24 | (0.04,1.36) | 0.1072 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.2.13: 1**

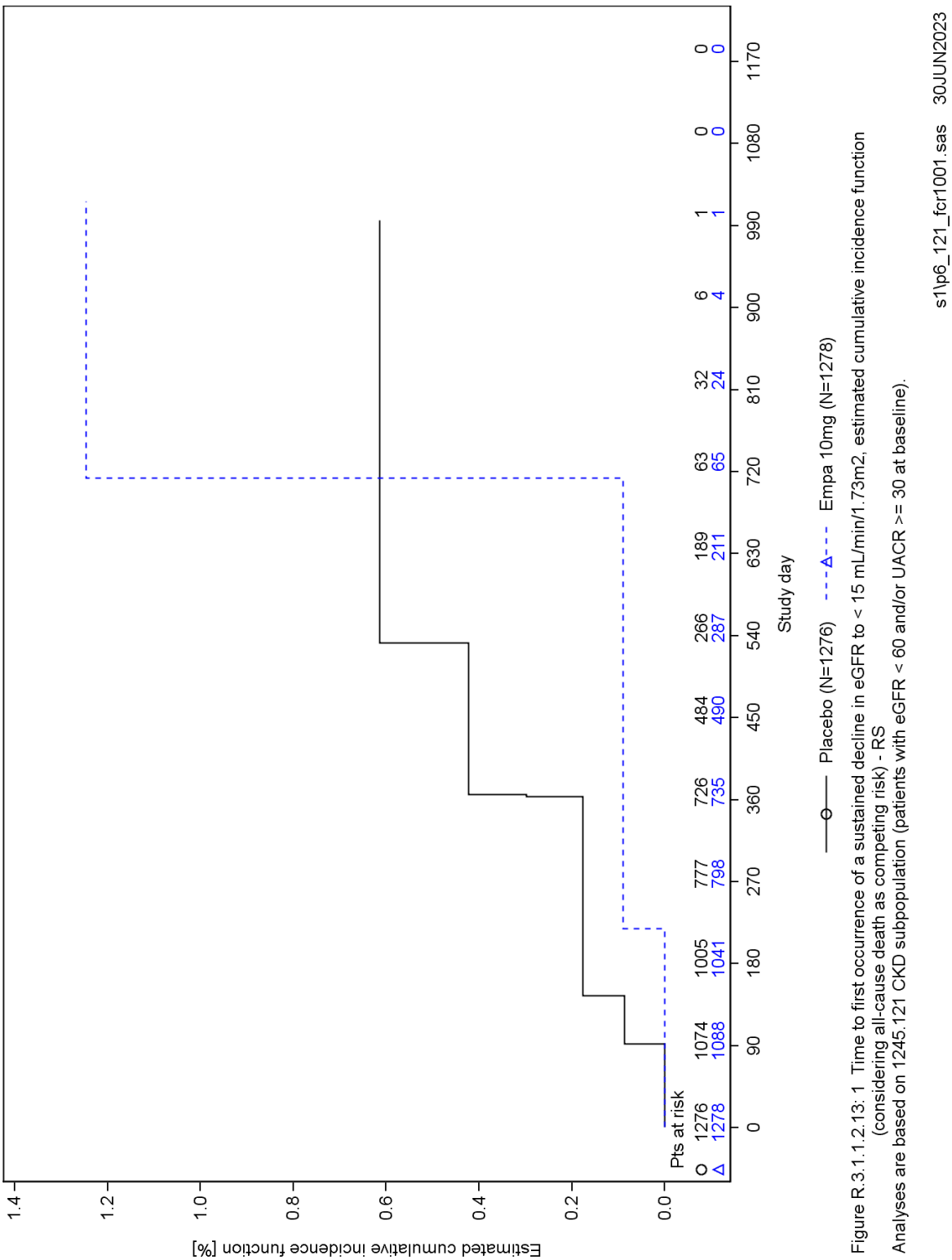


Figure R.3.1.1.2.13: 1 Time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.3.1.1.2.14**

R.3.1.1.2.14 Time to first occurrence of acute kidney injury

Table R.3.1.1.2.14: 1 Cox Regression for time to first occurrence of acute kidney injury until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 53 | 4.2 | 3.21 | 1278 | 38 | 3.0 | 2.27 | 0.67 | (0.44, 1.02) | 0.0600 | |
| Sex | | | | | | | | | | | | 0.9478 |
| Male | 959 | 42 | 4.4 | 3.36 | 975 | 30 | 3.1 | 2.34 | 0.66 | (0.42, 1.06) | 0.0887 | |
| Female | 317 | 11 | 3.5 | 2.76 | 303 | 8 | 2.6 | 2.03 | 0.69 | (0.28, 1.71) | 0.4217 | |
| Age [years] | | | | | | | | | | | | 0.4887 |
| <65 | 436 | 17 | 3.9 | 3.02 | 392 | 13 | 3.3 | 2.57 | 0.83 | (0.40, 1.72) | 0.6251 | |
| >=65 | 840 | 36 | 4.3 | 3.32 | 886 | 25 | 2.8 | 2.14 | 0.61 | (0.37, 1.02) | 0.0578 | |
| Region | | | | | | | | | | | | 0.9230 |
| North America | 161 | 18 | 11.2 | 8.88 | 159 | 17 | 10.7 | 7.49 | 0.85 | (0.43, 1.66) | 0.6300 | |
| Latin America | 420 | 16 | 3.8 | 3.21 | 440 | 9 | 2.0 | 1.71 | 0.53 | (0.23, 1.19) | 0.1246 | |
| Europe | 471 | 18 | 3.8 | 2.84 | 467 | 11 | 2.4 | 1.75 | 0.59 | (0.28, 1.26) | 0.1729 | |
| Asia | 174 | 0 | 0 | 0.00 | 165 | 1 | 0.6 | 0.43 | >999.99 | | 0.9823 | |
| Other | 50 | 1 | 2.0 | 1.54 | 47 | 0 | 0 | 0.00 | <0.01 | | 0.9903 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2517 |
| Diabetic | 696 | 28 | 4.0 | 3.08 | 698 | 24 | 3.4 | 2.65 | 0.83 | (0.48, 1.43) | 0.4939 | |
| Non-Diabetic | 580 | 25 | 4.3 | 3.38 | 580 | 14 | 2.4 | 1.82 | 0.50 | (0.26, 0.97) | 0.0393 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7904 |
| <30 | 890 | 31 | 3.5 | 2.65 | 836 | 21 | 2.5 | 1.93 | 0.69 | (0.39, 1.20) | 0.1851 | |
| >=30 | 386 | 22 | 5.7 | 4.59 | 442 | 17 | 3.8 | 2.91 | 0.61 | (0.32, 1.16) | 0.1308 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3124 |
| <130 | 859 | 42 | 4.9 | 3.84 | 834 | 26 | 3.1 | 2.41 | 0.59 | (0.36, 0.97) | 0.0360 | |
| >=130 | 417 | 11 | 2.6 | 1.98 | 444 | 12 | 2.7 | 2.01 | 0.97 | (0.43, 2.20) | 0.9379 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.9417 |
| <75 | 720 | 37 | 5.1 | 4.00 | 678 | 26 | 3.8 | 2.98 | 0.70 | (0.42, 1.16) | 0.1692 | |
| 75 to <85 | 348 | 11 | 3.2 | 2.43 | 382 | 9 | 2.4 | 1.78 | 0.69 | (0.28, 1.66) | 0.4020 | |
| >=85 | 208 | 5 | 2.4 | 1.84 | 218 | 3 | 1.4 | 1.01 | 0.54 | (0.13, 2.25) | 0.3955 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

Table R.3.1.1.2.14: 1 Cox Regression for time to first occurrence of acute kidney injury until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.0404 |
| <30 | 90 | 3 | 3.3 | 2.91 | 115 | 12 | 10.4 | 8.22 | 2.85 | (0.80,10.14) | 0.1064 | |
| 30 to <45 | 349 | 21 | 6.0 | 4.66 | 345 | 10 | 2.9 | 2.22 | 0.46 | (0.21, 0.97) | 0.0409 | |
| >=45 | 837 | 29 | 3.5 | 2.65 | 818 | 16 | 2.0 | 1.49 | 0.53 | (0.29, 0.98) | 0.0434 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0672 |
| Normal (<30) | 452 | 16 | 3.5 | 2.74 | 456 | 15 | 3.3 | 2.43 | 0.88 | (0.44, 1.79) | 0.7319 | |
| Microalbuminuria (30 to <=300) | 628 | 29 | 4.6 | 3.59 | 608 | 12 | 2.0 | 1.52 | 0.40 | (0.20, 0.78) | 0.0072 | |
| Macroalbuminuria (>300) | 189 | 6 | 3.2 | 2.40 | 207 | 11 | 5.3 | 4.26 | 1.50 | (0.55, 4.08) | 0.4247 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2158 |
| Low, moderate or high | 953 | 34 | 3.6 | 2.76 | 947 | 20 | 2.1 | 1.60 | 0.55 | (0.32, 0.96) | 0.0356 | |
| Very high | 317 | 17 | 5.4 | 4.15 | 325 | 18 | 5.5 | 4.29 | 0.95 | (0.49, 1.86) | 0.8913 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9760 |
| No | 161 | 5 | 3.1 | 2.33 | 168 | 5 | 3.0 | 2.19 | 0.69 | (0.20, 2.40) | 0.5570 | |
| Yes | 1115 | 48 | 4.3 | 3.35 | 1110 | 33 | 3.0 | 2.28 | 0.67 | (0.43, 1.05) | 0.0820 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.2923 |
| No | 62 | 7 | 11.3 | 8.92 | 72 | 3 | 4.2 | 3.44 | 0.33 | (0.08, 1.30) | 0.1127 | |
| Yes | 1214 | 46 | 3.8 | 2.93 | 1206 | 35 | 2.9 | 2.21 | 0.72 | (0.46, 1.11) | 0.1367 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.4694 |
| No | 46 | 2 | 4.3 | 3.35 | 57 | 1 | 1.8 | 1.36 | 0.28 | (0.03, 3.12) | 0.3015 | |
| Yes | 1230 | 51 | 4.1 | 3.21 | 1221 | 37 | 3.0 | 2.31 | 0.69 | (0.45, 1.06) | 0.0908 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

**Figure R.3.1.1.2.14: 1**

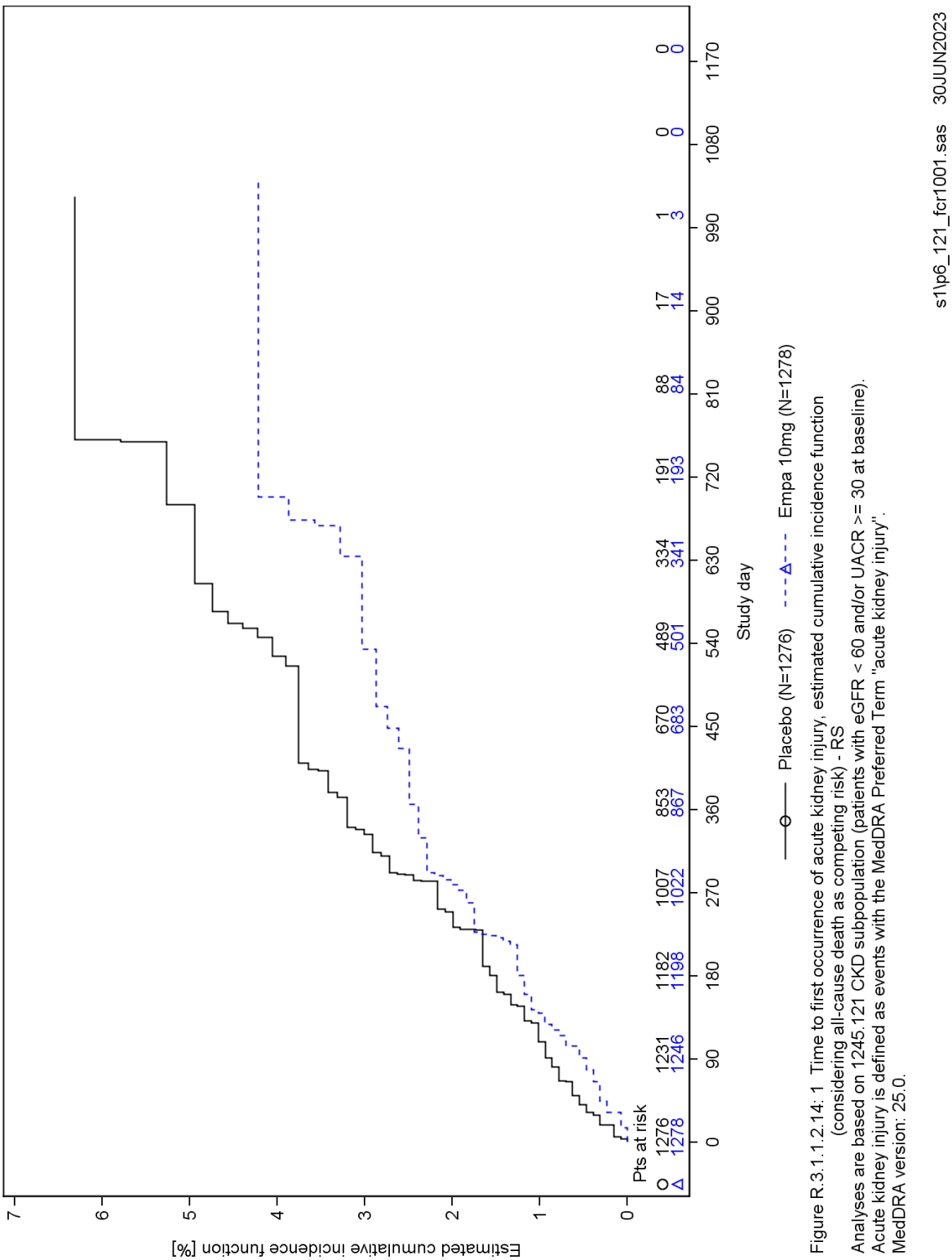


Figure R.3.1.1.2.14: 1 Time to first occurrence of acute kidney injury, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

**Figure R.3.1.1.2.14: 2**

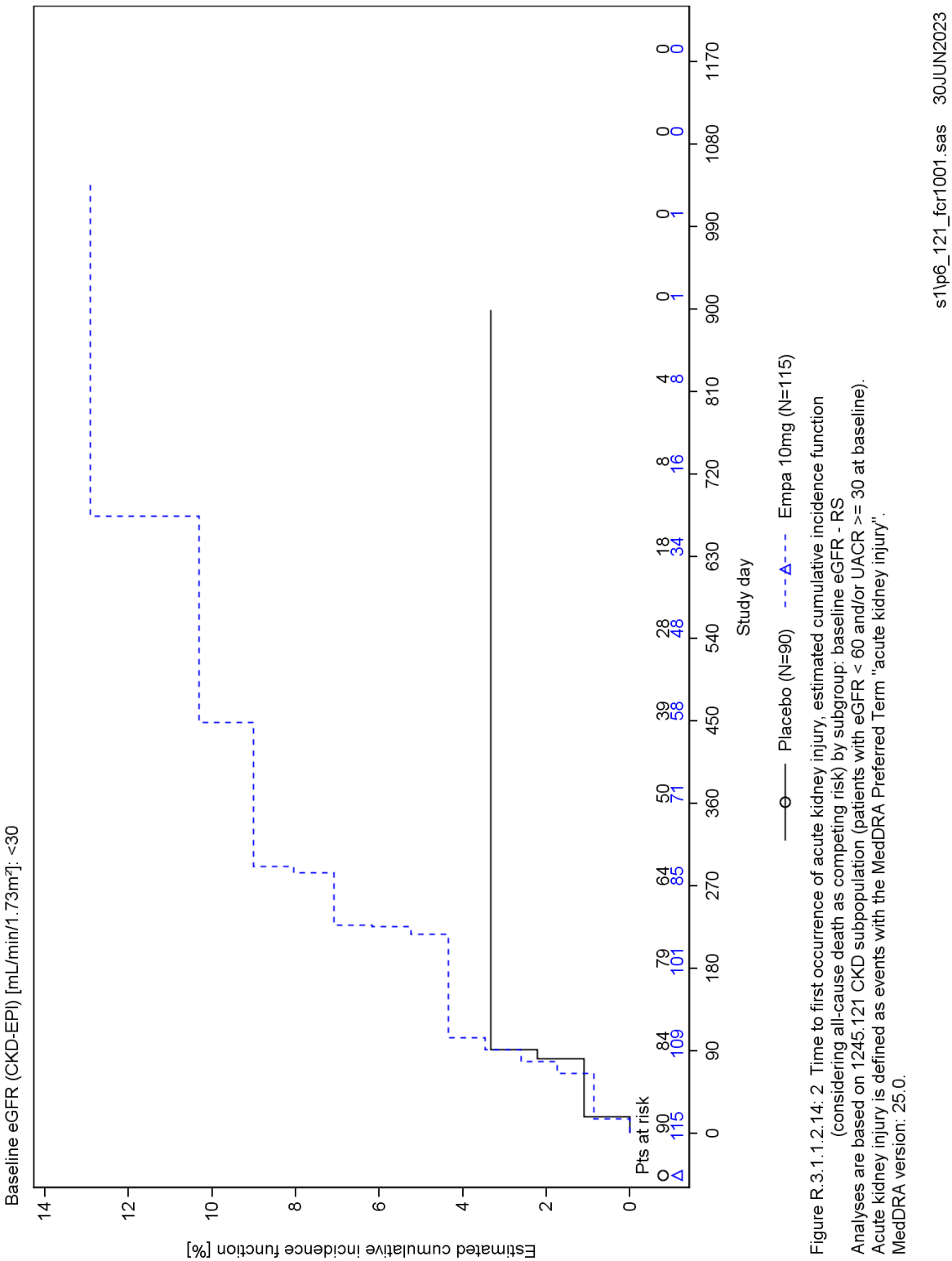


Figure R.3.1.1.2.14: 2 Time to first occurrence of acute kidney injury, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline eGFR - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

**Figure R.3.1.1.2.14: 2**

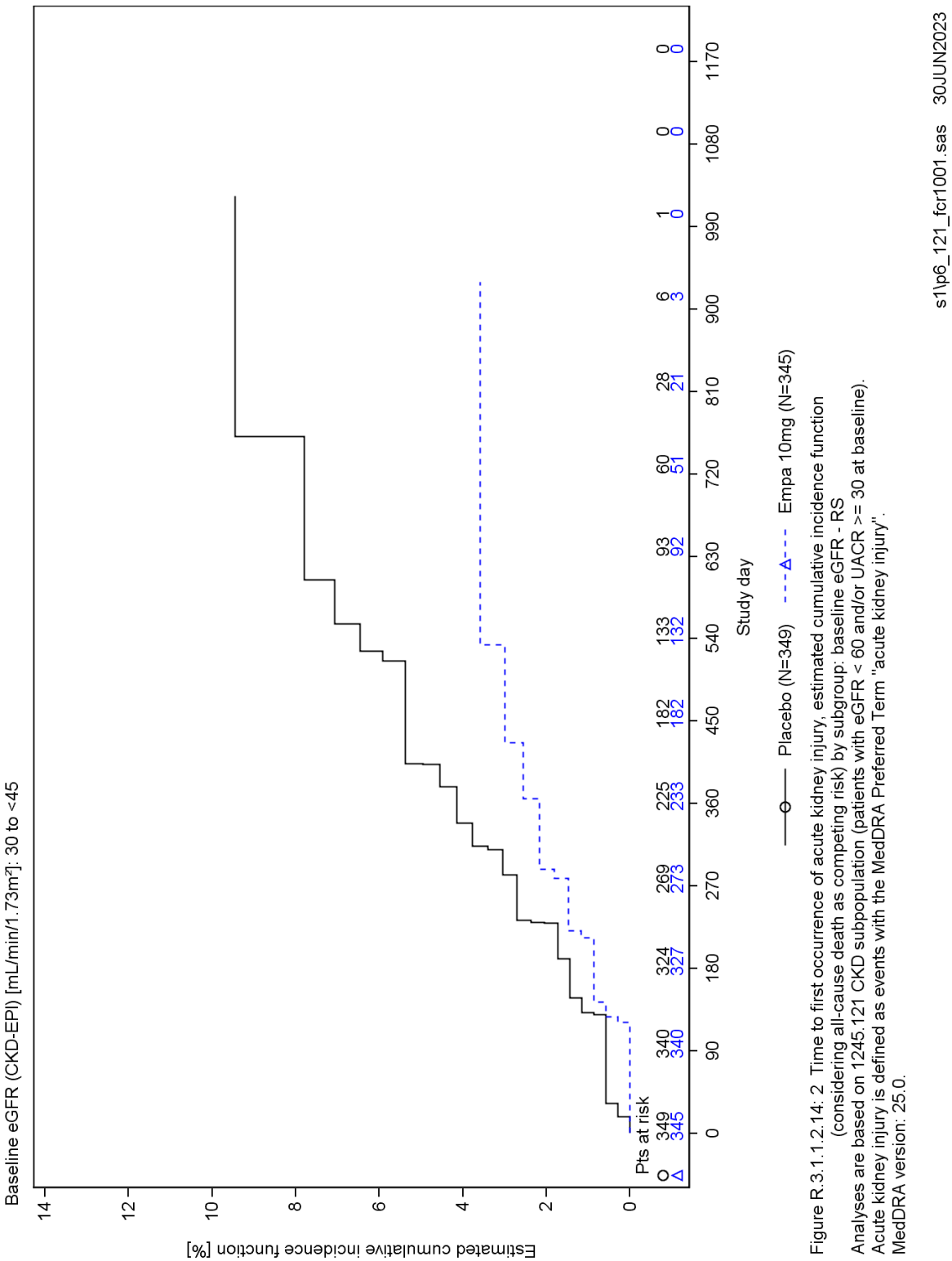


Figure R.3.1.1.2.14: 2 Time to first occurrence of acute kidney injury, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline eGFR - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

**Figure R.3.1.1.2.14: 2**

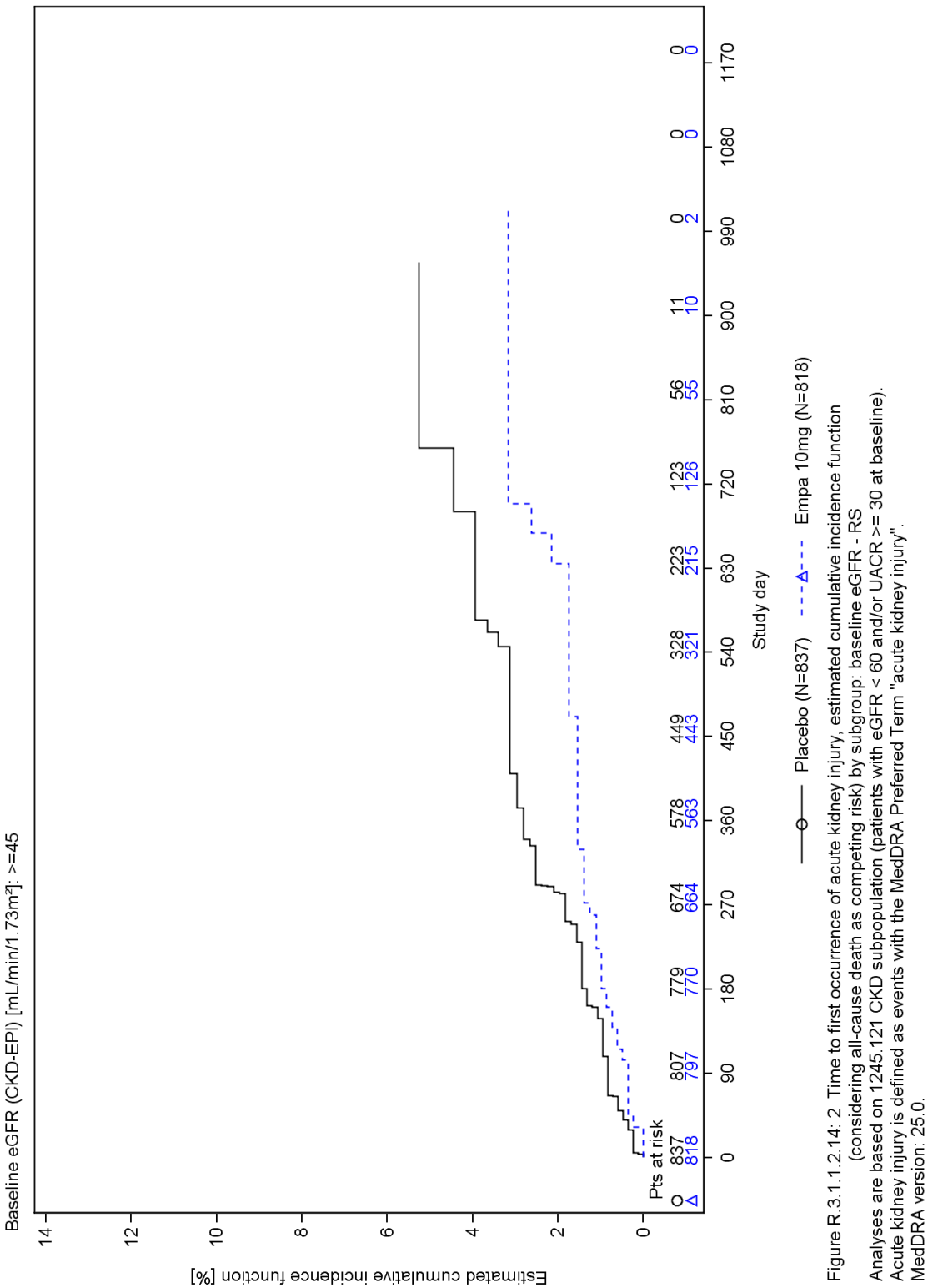


Figure R.3.1.1.2.14: 2 Time to first occurrence of acute kidney injury, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline eGFR - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

**R.3.1.1.3**

R.3.1.1.3.1 Time to first occurrence of aan adjudicated major cardiovascular event

Table R.3.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 376 | 29.5 | 25.93 | 1278 | 297 | 23.2 | 19.31 | 0.75 | (0.64,0.87) | 0.0002 | |
| Sex | | | | | | | | | | | | 0.0704 |
| Male | 959 | 286 | 29.8 | 26.09 | 975 | 244 | 25.0 | 20.86 | 0.80 | (0.68,0.95) | 0.0123 | |
| Female | 317 | 90 | 28.4 | 25.43 | 303 | 53 | 17.5 | 14.39 | 0.57 | (0.40,0.79) | 0.0010 | |
| Age [years] | | | | | | | | | | | | 0.3987 |
| <65 | 436 | 141 | 32.3 | 29.63 | 392 | 92 | 23.5 | 19.86 | 0.68 | (0.52,0.89) | 0.0046 | |
| >=65 | 840 | 235 | 28.0 | 24.12 | 886 | 205 | 23.1 | 19.07 | 0.79 | (0.65,0.95) | 0.0117 | |
| Region | | | | | | | | | | | | 0.4846 |
| North America | 161 | 57 | 35.4 | 32.74 | 159 | 44 | 27.7 | 21.52 | 0.70 | (0.47,1.04) | 0.0771 | |
| Latin America | 420 | 118 | 28.1 | 26.40 | 440 | 97 | 22.0 | 19.69 | 0.75 | (0.57,0.98) | 0.0351 | |
| Europe | 471 | 124 | 26.3 | 21.85 | 467 | 109 | 23.3 | 19.16 | 0.87 | (0.67,1.13) | 0.2954 | |
| Asia | 174 | 64 | 36.8 | 31.88 | 165 | 41 | 24.8 | 19.05 | 0.60 | (0.41,0.89) | 0.0116 | |
| Other | 50 | 13 | 26.0 | 21.33 | 47 | 6 | 12.8 | 10.55 | 0.48 | (0.18,1.25) | 0.1320 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9887 |
| Diabetic | 696 | 224 | 32.2 | 28.51 | 698 | 175 | 25.1 | 21.13 | 0.75 | (0.61,0.91) | 0.0040 | |
| Non-Diabetic | 580 | 152 | 26.2 | 22.87 | 580 | 122 | 21.0 | 17.19 | 0.75 | (0.59,0.95) | 0.0161 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.4250 |
| <30 | 890 | 256 | 28.8 | 24.69 | 836 | 178 | 21.3 | 17.55 | 0.71 | (0.58,0.85) | 0.0004 | |
| >=30 | 386 | 120 | 31.1 | 29.02 | 442 | 119 | 26.9 | 22.72 | 0.80 | (0.62,1.04) | 0.0906 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.9924 |
| <130 | 859 | 272 | 31.7 | 28.41 | 834 | 209 | 25.1 | 21.44 | 0.75 | (0.63,0.90) | 0.0019 | |
| >=130 | 417 | 104 | 24.9 | 21.10 | 444 | 88 | 19.8 | 15.63 | 0.75 | (0.57,1.00) | 0.0498 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2140 |
| <75 | 720 | 214 | 29.7 | 25.84 | 678 | 172 | 25.4 | 21.76 | 0.83 | (0.68,1.02) | 0.0749 | |
| 75 to <85 | 348 | 104 | 29.9 | 26.58 | 382 | 87 | 22.8 | 18.60 | 0.70 | (0.53,0.93) | 0.0148 | |
| >=85 | 208 | 58 | 27.9 | 25.14 | 218 | 38 | 17.4 | 13.58 | 0.57 | (0.38,0.85) | 0.0065 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs) adjudicated stroke or adjudicated hospitalization for heart failure.

Table R.3.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2401 |
| <30 | 90 | 35 | 38.9 | 41.40 | 115 | 38 | 33.0 | 28.10 | 0.70 | (0.44,1.11) | 0.1303 | |
| 30 to <45 | 349 | 101 | 28.9 | 24.51 | 345 | 91 | 26.4 | 22.29 | 0.91 | (0.68,1.20) | 0.4986 | |
| >=45 | 837 | 240 | 28.7 | 25.17 | 818 | 168 | 20.5 | 16.89 | 0.68 | (0.55,0.82) | <0.0001 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9345 |
| Normal (<30) | 452 | 96 | 21.2 | 17.86 | 456 | 81 | 17.8 | 13.86 | 0.77 | (0.58,1.04) | 0.0915 | |
| Microalbuminuria (30 to <=300) | 628 | 204 | 32.5 | 28.67 | 608 | 147 | 24.2 | 20.51 | 0.73 | (0.59,0.90) | 0.0036 | |
| Macroalbuminuria (>300) | 189 | 72 | 38.1 | 36.83 | 207 | 68 | 32.9 | 29.66 | 0.77 | (0.55,1.07) | 0.1212 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0632 |
| Low, moderate or high | 953 | 263 | 27.6 | 24.05 | 947 | 190 | 20.1 | 16.38 | 0.68 | (0.57,0.82) | <0.0001 | |
| Very high | 317 | 109 | 34.4 | 30.89 | 325 | 107 | 32.9 | 28.78 | 0.93 | (0.71,1.22) | 0.6017 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.4847 |
| No | 161 | 52 | 32.3 | 27.65 | 168 | 49 | 29.2 | 24.27 | 0.85 | (0.57,1.26) | 0.4121 | |
| Yes | 1115 | 324 | 29.1 | 25.67 | 1110 | 248 | 22.3 | 18.56 | 0.73 | (0.62,0.86) | 0.0002 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4203 |
| No | 62 | 19 | 30.6 | 26.64 | 72 | 20 | 27.8 | 25.21 | 0.96 | (0.51,1.80) | 0.8976 | |
| Yes | 1214 | 357 | 29.4 | 25.89 | 1206 | 277 | 23.0 | 18.99 | 0.74 | (0.63,0.86) | 0.0001 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3759 |
| No | 46 | 10 | 21.7 | 18.04 | 57 | 6 | 10.5 | 8.49 | 0.48 | (0.17,1.31) | 0.1519 | |
| Yes | 1230 | 366 | 29.8 | 26.24 | 1221 | 291 | 23.8 | 19.83 | 0.76 | (0.65,0.88) | 0.0004 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs) adjudicated stroke or adjudicated hospitalization for heart failure.

**Figure R.3.1.1.3.1: 1**

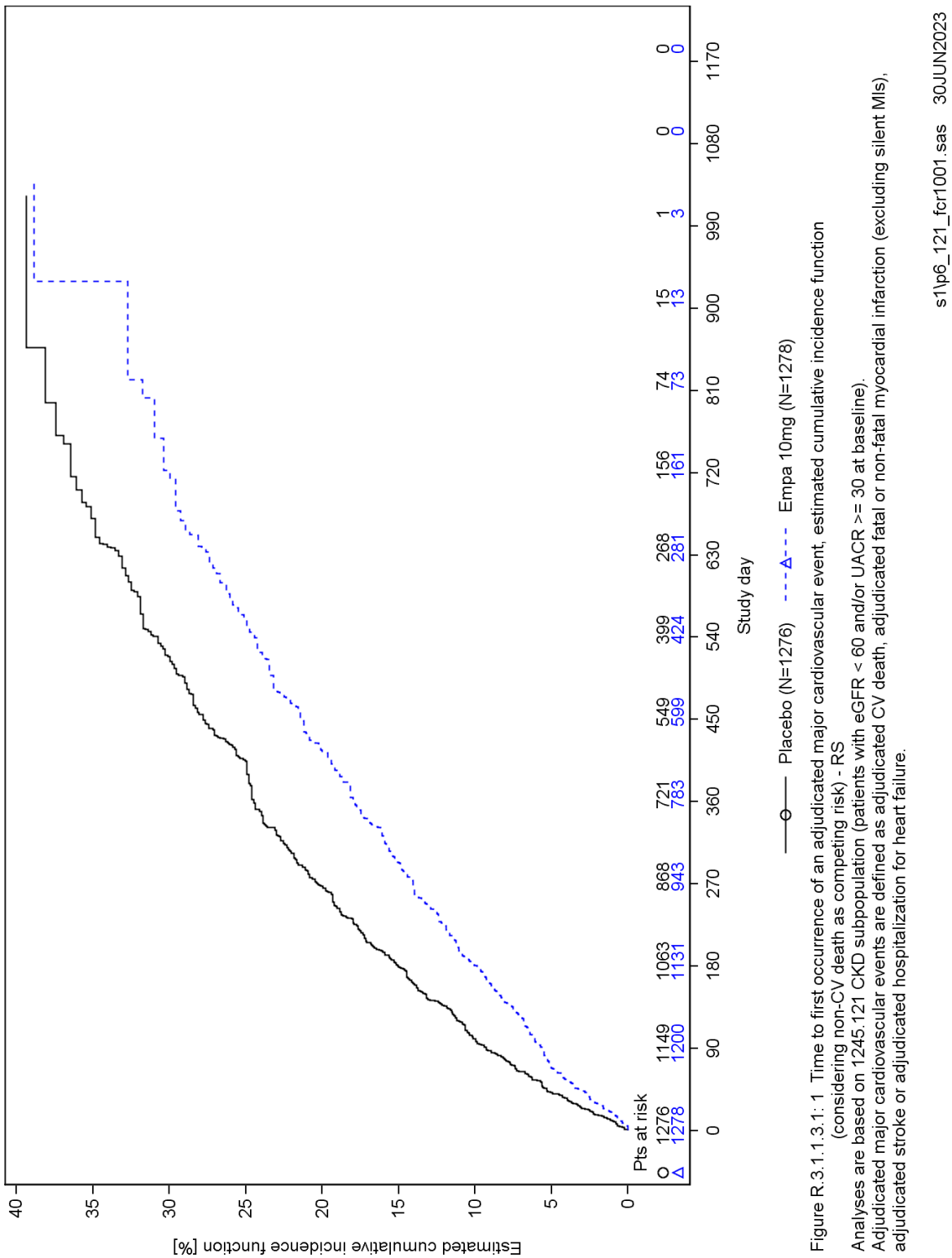


Figure R.3.1.1.3.1: 1 Time to first occurrence of an adjudicated major cardiovascular event, estimated cumulative incidence function (considering non-CV death as competing risk) - RS

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.

R.3.1.1.3.2 Time to first occurrence of an adjudicated myocardial infarction

Table R.3.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 12 | 0.9 | 0.72 | 1278 | 14 | 1.1 | 0.83 | 1.14 | (0.52, 2.47) | 0.7450 | |
| Sex | | | | | | | | | | | | 0.2617 |
| Male | 959 | 6 | 0.6 | 0.47 | 975 | 10 | 1.0 | 0.78 | 1.63 | (0.59, 4.51) | 0.3444 | |
| Female | 317 | 6 | 1.9 | 1.50 | 303 | 4 | 1.3 | 1.01 | 0.64 | (0.18, 2.30) | 0.4965 | |
| Age [years] | | | | | | | | | | | | 0.9460 |
| <65 | 436 | 3 | 0.7 | 0.53 | 392 | 3 | 0.8 | 0.58 | 1.22 | (0.24, 6.06) | 0.8114 | |
| >=65 | 840 | 9 | 1.1 | 0.82 | 886 | 11 | 1.2 | 0.94 | 1.14 | (0.47, 2.77) | 0.7700 | |
| Region | | | | | | | | | | | | 0.9999 |
| North America | 161 | 5 | 3.1 | 2.38 | 159 | 4 | 2.5 | 1.73 | 0.77 | (0.20, 2.90) | 0.6983 | |
| Latin America | 420 | 0 | 0 | 0.00 | 440 | 4 | 0.9 | 0.76 | >999.99 | | 0.9892 | |
| Europe | 471 | 6 | 1.3 | 0.95 | 467 | 5 | 1.1 | 0.79 | 0.85 | (0.26, 2.79) | 0.7915 | |
| Asia | 174 | 1 | 0.6 | 0.40 | 165 | 1 | 0.6 | 0.43 | 0.94 | (0.06,15.18) | 0.9675 | |
| Other | 50 | 0 | 0 | 0.00 | 47 | 0 | 0 | 0.00 | 0.90 | | 1.0000 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.8370 |
| Diabetic | 696 | 4 | 0.6 | 0.43 | 698 | 5 | 0.7 | 0.55 | 1.26 | (0.34, 4.71) | 0.7290 | |
| Non-Diabetic | 580 | 8 | 1.4 | 1.07 | 580 | 9 | 1.6 | 1.17 | 1.06 | (0.41, 2.77) | 0.8992 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2075 |
| <30 | 890 | 10 | 1.1 | 0.85 | 836 | 8 | 1.0 | 0.73 | 0.81 | (0.32, 2.07) | 0.6589 | |
| >=30 | 386 | 2 | 0.5 | 0.41 | 442 | 6 | 1.4 | 1.03 | 2.67 | (0.54,13.25) | 0.2297 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3497 |
| <130 | 859 | 8 | 0.9 | 0.72 | 834 | 6 | 0.7 | 0.56 | 0.79 | (0.27, 2.30) | 0.6707 | |
| >=130 | 417 | 4 | 1.0 | 0.72 | 444 | 8 | 1.8 | 1.33 | 1.71 | (0.51, 5.77) | 0.3834 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.9693 |
| <75 | 720 | 10 | 1.4 | 1.07 | 678 | 10 | 1.5 | 1.15 | 1.06 | (0.44, 2.56) | 0.9038 | |
| 75 to <85 | 348 | 2 | 0.6 | 0.43 | 382 | 3 | 0.8 | 0.59 | 1.36 | (0.23, 8.18) | 0.7348 | |
| >=85 | 208 | 0 | 0 | 0.00 | 218 | 1 | 0.5 | 0.33 | >999.99 | | 0.9911 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

Table R.3.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.5985 |
| <30 | 90 | 3 | 3.3 | 2.96 | 115 | 2 | 1.7 | 1.33 | 0.52 | (0.09, 3.18) | 0.4834 | |
| 30 to <45 | 349 | 3 | 0.9 | 0.65 | 345 | 3 | 0.9 | 0.66 | 1.00 | (0.20, 4.95) | 0.9964 | |
| >=45 | 837 | 6 | 0.7 | 0.54 | 818 | 9 | 1.1 | 0.83 | 1.52 | (0.54, 4.30) | 0.4281 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8525 |
| Normal (<30) | 452 | 4 | 0.9 | 0.68 | 456 | 3 | 0.7 | 0.48 | 0.77 | (0.17, 3.47) | 0.7338 | |
| Microalbuminuria (30 to <=300) | 628 | 6 | 1.0 | 0.73 | 608 | 8 | 1.3 | 1.01 | 1.27 | (0.43, 3.69) | 0.6665 | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 0.80 | 207 | 3 | 1.4 | 1.14 | 1.32 | (0.22, 8.06) | 0.7609 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.6585 |
| Low, moderate or high | 953 | 8 | 0.8 | 0.64 | 947 | 8 | 0.8 | 0.64 | 1.00 | (0.37, 2.67) | 0.9946 | |
| Very high | 317 | 4 | 1.3 | 0.96 | 325 | 6 | 1.8 | 1.41 | 1.43 | (0.40, 5.11) | 0.5790 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.1575 |
| No | 161 | 3 | 1.9 | 1.39 | 168 | 1 | 0.6 | 0.43 | 0.25 | (0.03, 2.47) | 0.2371 | |
| Yes | 1115 | 9 | 0.8 | 0.62 | 1110 | 13 | 1.2 | 0.90 | 1.46 | (0.62, 3.43) | 0.3844 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9927 |
| No | 62 | 0 | 0 | 0.00 | 72 | 1 | 1.4 | 1.12 | >999.99 | | 0.9927 | |
| Yes | 1214 | 12 | 1.0 | 0.76 | 1206 | 13 | 1.1 | 0.82 | 1.08 | (0.49, 2.37) | 0.8557 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9912 |
| No | 46 | 1 | 2.2 | 1.64 | 57 | 0 | 0 | 0.00 | <0.01 | | 0.9913 | |
| Yes | 1230 | 11 | 0.9 | 0.68 | 1221 | 14 | 1.1 | 0.87 | 1.25 | (0.56, 2.75) | 0.5879 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

**Figure R.3.1.1.3.2: 1**

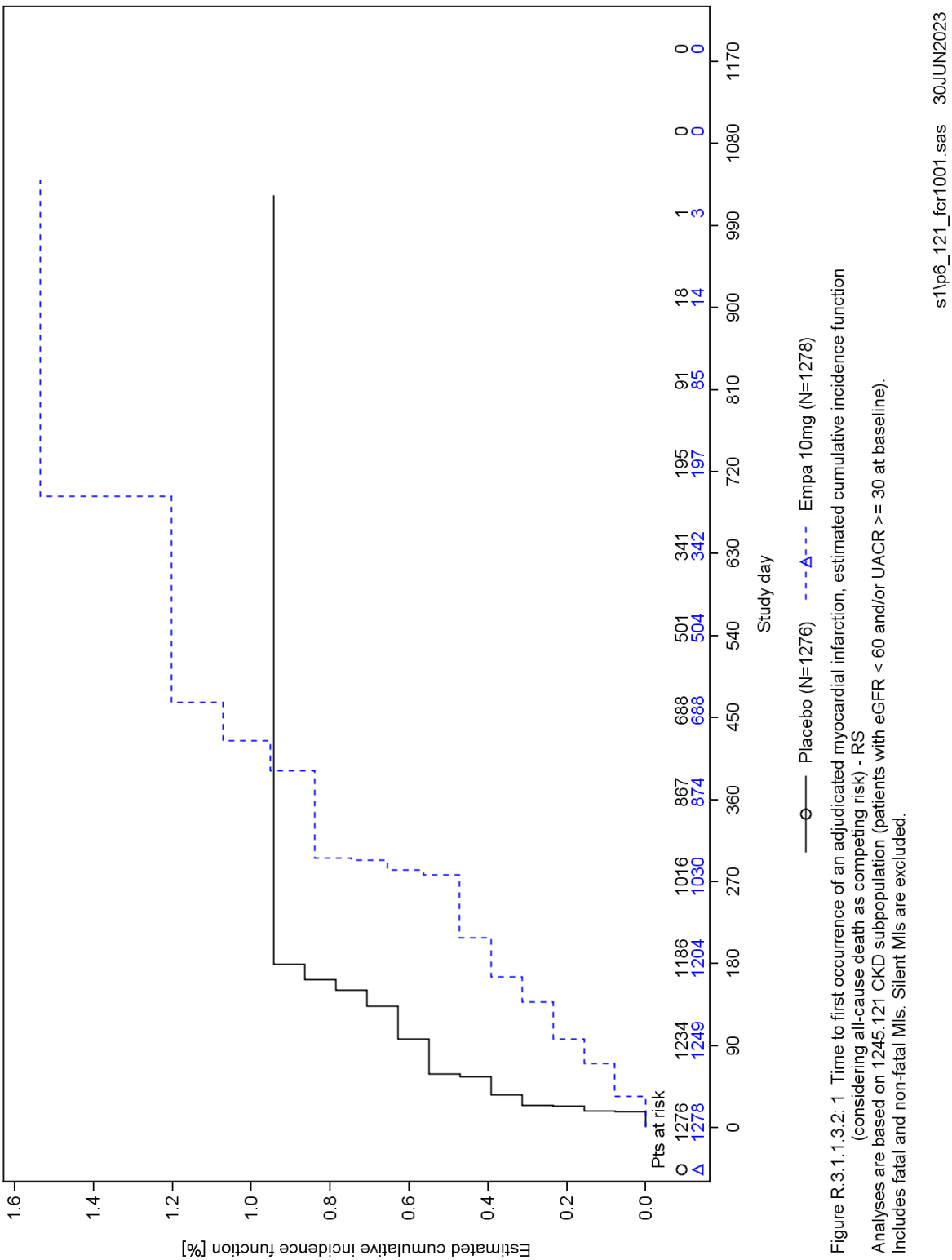


Figure R.3.1.1.3.2: 1 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

R.3.1.1.3.3 Time to first occurrence of an adjudicated stroke

Table R.3.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 20 | 1.6 | 1.20 | 1278 | 29 | 2.3 | 1.73 | 1.44 | (0.81, 2.54) | 0.2120 | |
| Sex | | | | | | | | | | | | 0.1002 |
| Male | 959 | 12 | 1.3 | 0.95 | 975 | 24 | 2.5 | 1.88 | 1.96 | (0.98, 3.92) | 0.0585 | |
| Female | 317 | 8 | 2.5 | 1.99 | 303 | 5 | 1.7 | 1.27 | 0.65 | (0.21, 1.98) | 0.4450 | |
| Age [years] | | | | | | | | | | | | 0.2943 |
| <65 | 436 | 4 | 0.9 | 0.70 | 392 | 9 | 2.3 | 1.77 | 2.46 | (0.76, 8.01) | 0.1352 | |
| >=65 | 840 | 16 | 1.9 | 1.46 | 886 | 20 | 2.3 | 1.72 | 1.19 | (0.62, 2.30) | 0.6019 | |
| Region | | | | | | | | | | | | 0.3483 |
| North America | 161 | 4 | 2.5 | 1.88 | 159 | 3 | 1.9 | 1.30 | 0.67 | (0.15, 3.00) | 0.5998 | |
| Latin America | 420 | 4 | 1.0 | 0.79 | 440 | 12 | 2.7 | 2.29 | 2.95 | (0.95, 9.16) | 0.0617 | |
| Europe | 471 | 9 | 1.9 | 1.42 | 467 | 8 | 1.7 | 1.27 | 0.89 | (0.34, 2.32) | 0.8154 | |
| Asia | 174 | 2 | 1.1 | 0.80 | 165 | 6 | 3.6 | 2.62 | 3.19 | (0.64,15.84) | 0.1555 | |
| Other | 50 | 1 | 2.0 | 1.55 | 47 | 0 | 0 | 0.00 | <0.01 | | 0.9860 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3367 |
| Diabetic | 696 | 10 | 1.4 | 1.09 | 698 | 18 | 2.6 | 1.99 | 1.84 | (0.85, 3.99) | 0.1212 | |
| Non-Diabetic | 580 | 10 | 1.7 | 1.34 | 580 | 11 | 1.9 | 1.43 | 1.05 | (0.44, 2.47) | 0.9172 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7048 |
| <30 | 890 | 12 | 1.3 | 1.02 | 836 | 17 | 2.0 | 1.56 | 1.53 | (0.73, 3.20) | 0.2616 | |
| >=30 | 386 | 8 | 2.1 | 1.65 | 442 | 12 | 2.7 | 2.06 | 1.22 | (0.50, 2.99) | 0.6634 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.2727 |
| <130 | 859 | 12 | 1.4 | 1.08 | 834 | 21 | 2.5 | 1.96 | 1.81 | (0.89, 3.68) | 0.1019 | |
| >=130 | 417 | 8 | 1.9 | 1.44 | 444 | 8 | 1.8 | 1.33 | 0.92 | (0.34, 2.45) | 0.8634 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3744 |
| <75 | 720 | 11 | 1.5 | 1.17 | 678 | 20 | 2.9 | 2.32 | 1.97 | (0.94, 4.11) | 0.0723 | |
| 75 to <85 | 348 | 6 | 1.7 | 1.31 | 382 | 7 | 1.8 | 1.37 | 1.07 | (0.36, 3.19) | 0.9039 | |
| >=85 | 208 | 3 | 1.4 | 1.10 | 218 | 2 | 0.9 | 0.67 | 0.58 | (0.10, 3.47) | 0.5487 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.3.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1316 |
| <30 | 90 | 1 | 1.1 | 0.97 | 115 | 3 | 2.6 | 1.99 | 2.17 | (0.22,20.88) | 0.5040 | |
| 30 to <45 | 349 | 9 | 2.6 | 1.96 | 345 | 5 | 1.4 | 1.10 | 0.56 | (0.19, 1.68) | 0.3022 | |
| >=45 | 837 | 10 | 1.2 | 0.91 | 818 | 21 | 2.6 | 1.97 | 2.15 | (1.01, 4.58) | 0.0463 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4328 |
| Normal (<30) | 452 | 8 | 1.8 | 1.36 | 456 | 8 | 1.8 | 1.30 | 0.98 | (0.37, 2.63) | 0.9739 | |
| Microalbuminuria (30 to <=300) | 628 | 9 | 1.4 | 1.10 | 608 | 14 | 2.3 | 1.78 | 1.58 | (0.68, 3.65) | 0.2878 | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 0.79 | 207 | 7 | 3.4 | 2.68 | 3.29 | (0.68,15.88) | 0.1386 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.6815 |
| Low, moderate or high | 953 | 12 | 1.3 | 0.96 | 947 | 20 | 2.1 | 1.61 | 1.65 | (0.81, 3.38) | 0.1696 | |
| Very high | 317 | 7 | 2.2 | 1.68 | 325 | 9 | 2.8 | 2.12 | 1.28 | (0.48, 3.44) | 0.6262 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9817 |
| No | 161 | 0 | 0 | 0.00 | 168 | 6 | 3.6 | 2.64 | >999.99 | | 0.9815 | |
| Yes | 1115 | 20 | 1.8 | 1.38 | 1110 | 23 | 2.1 | 1.59 | 1.14 | (0.63, 2.08) | 0.6677 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9828 |
| No | 62 | 0 | 0 | 0.00 | 72 | 2 | 2.8 | 2.28 | >999.99 | | 0.9824 | |
| Yes | 1214 | 20 | 1.6 | 1.26 | 1206 | 27 | 2.2 | 1.70 | 1.34 | (0.75, 2.39) | 0.3226 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.7055 |
| No | 46 | 1 | 2.2 | 1.64 | 57 | 1 | 1.8 | 1.33 | 0.85 | (0.05,13.78) | 0.9087 | |
| Yes | 1230 | 19 | 1.5 | 1.18 | 1221 | 28 | 2.3 | 1.75 | 1.47 | (0.82, 2.63) | 0.1947 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.3.3: 1**

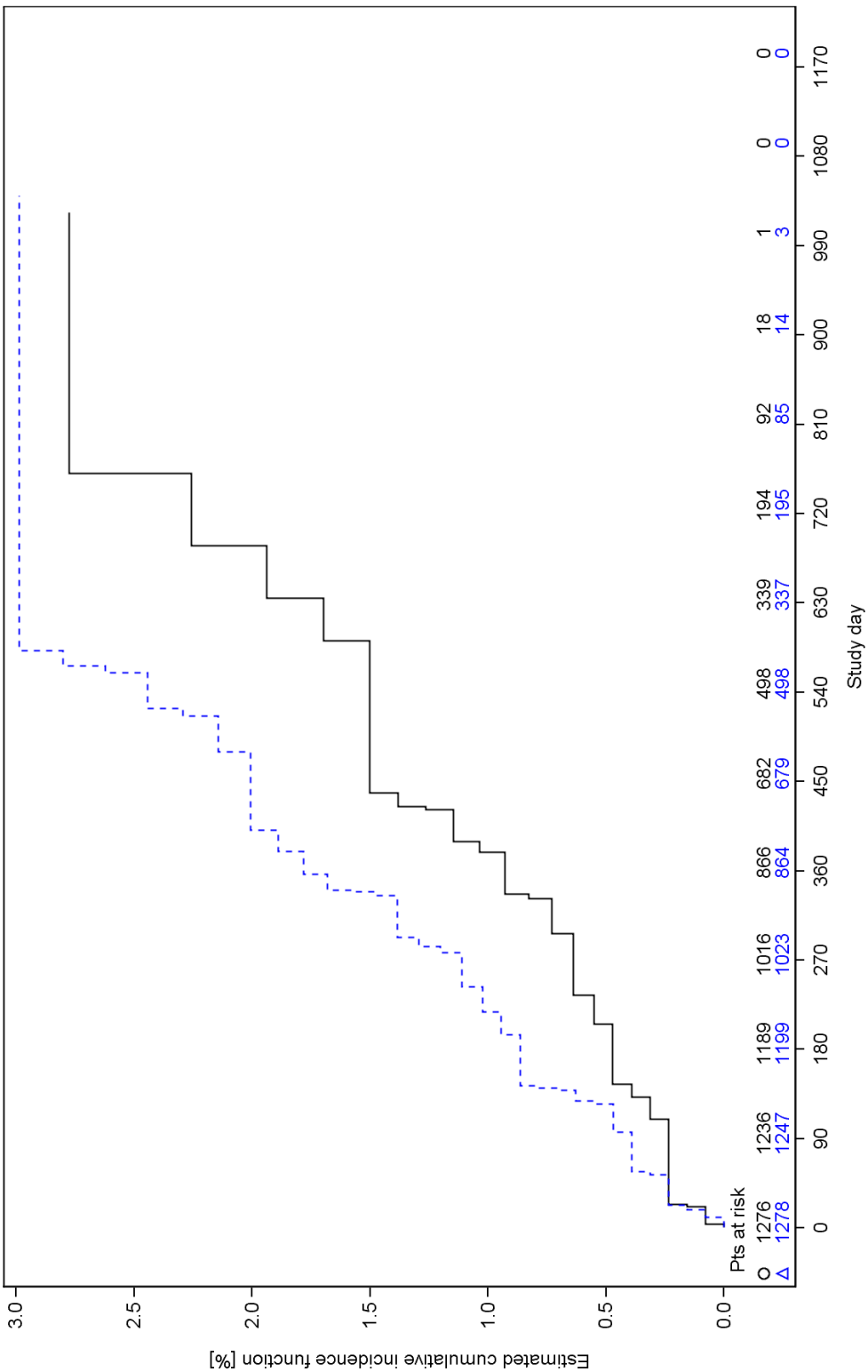


Figure R.3.1.1.3.3: 1 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.3.1.1.3.4 Time to first adjudicated hospitalization for heart failure

Table R.3.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 275 | 21.6 | 18.73 | 1278 | 199 | 15.6 | 12.76 | 0.69 | (0.57,0.83) | <0.0001 | |
| Sex | | | | | | | | | | | | 0.1755 |
| Male | 959 | 214 | 22.3 | 19.32 | 975 | 165 | 16.9 | 13.91 | 0.73 | (0.60,0.90) | 0.0027 | |
| Female | 317 | 61 | 19.2 | 16.93 | 303 | 34 | 11.2 | 9.09 | 0.53 | (0.35,0.81) | 0.0031 | |
| Age [years] | | | | | | | | | | | | 0.4149 |
| <65 | 436 | 113 | 25.9 | 23.56 | 392 | 67 | 17.1 | 14.36 | 0.63 | (0.46,0.85) | 0.0024 | |
| >=65 | 840 | 162 | 19.3 | 16.39 | 886 | 132 | 14.9 | 12.07 | 0.73 | (0.58,0.92) | 0.0083 | |
| Region | | | | | | | | | | | | 0.1113 |
| North America | 161 | 44 | 27.3 | 24.61 | 159 | 35 | 22.0 | 16.84 | 0.76 | (0.48,1.18) | 0.2202 | |
| Latin America | 420 | 84 | 20.0 | 18.65 | 440 | 57 | 13.0 | 11.32 | 0.61 | (0.44,0.86) | 0.0043 | |
| Europe | 471 | 84 | 17.8 | 14.60 | 467 | 77 | 16.5 | 13.42 | 0.91 | (0.67,1.24) | 0.5532 | |
| Asia | 174 | 56 | 32.2 | 27.83 | 165 | 26 | 15.8 | 11.91 | 0.44 | (0.27,0.70) | 0.0005 | |
| Other | 50 | 7 | 14.0 | 11.26 | 47 | 4 | 8.5 | 7.03 | 0.59 | (0.17,2.03) | 0.4076 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9674 |
| Diabetic | 696 | 167 | 24.0 | 20.98 | 698 | 119 | 17.0 | 14.17 | 0.69 | (0.54,0.87) | 0.0017 | |
| Non-Diabetic | 580 | 108 | 18.6 | 16.07 | 580 | 80 | 13.8 | 11.10 | 0.69 | (0.52,0.92) | 0.0124 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1585 |
| <30 | 890 | 185 | 20.8 | 17.68 | 836 | 112 | 13.4 | 10.89 | 0.61 | (0.48,0.77) | <0.0001 | |
| >=30 | 386 | 90 | 23.3 | 21.36 | 442 | 87 | 19.7 | 16.36 | 0.80 | (0.60,1.08) | 0.1438 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.9239 |
| <130 | 859 | 205 | 23.9 | 21.21 | 834 | 145 | 17.4 | 14.64 | 0.69 | (0.56,0.85) | 0.0006 | |
| >=130 | 417 | 70 | 16.8 | 13.95 | 444 | 54 | 12.2 | 9.48 | 0.70 | (0.49,1.00) | 0.0509 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3931 |
| <75 | 720 | 151 | 21.0 | 17.98 | 678 | 112 | 16.5 | 13.83 | 0.76 | (0.60,0.97) | 0.0302 | |
| 75 to <85 | 348 | 79 | 22.7 | 20.00 | 382 | 60 | 15.7 | 12.76 | 0.64 | (0.46,0.90) | 0.0095 | |
| >=85 | 208 | 45 | 21.6 | 19.31 | 218 | 27 | 12.4 | 9.64 | 0.54 | (0.33,0.87) | 0.0112 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.3.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.0821 |
| <30 | 90 | 24 | 26.7 | 27.86 | 115 | 28 | 24.3 | 20.16 | 0.77 | (0.44,1.32) | 0.3372 | |
| 30 to <45 | 349 | 68 | 19.5 | 16.22 | 345 | 62 | 18.0 | 15.05 | 0.92 | (0.65,1.30) | 0.6434 | |
| >=45 | 837 | 183 | 21.9 | 19.01 | 818 | 109 | 13.3 | 10.80 | 0.58 | (0.46,0.73) | <0.0001 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.5236 |
| Normal (<30) | 452 | 67 | 14.8 | 12.31 | 456 | 52 | 11.4 | 8.77 | 0.71 | (0.49,1.01) | 0.0594 | |
| Microalbuminuria (30 to <=300) | 628 | 145 | 23.1 | 20.16 | 608 | 105 | 17.3 | 14.47 | 0.74 | (0.58,0.96) | 0.0219 | |
| Macroalbuminuria (>300) | 189 | 60 | 31.7 | 30.15 | 207 | 42 | 20.3 | 17.93 | 0.57 | (0.38,0.84) | 0.0051 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0293 |
| Low, moderate or high | 953 | 193 | 20.3 | 17.47 | 947 | 122 | 12.9 | 10.39 | 0.60 | (0.48,0.76) | <0.0001 | |
| Very high | 317 | 79 | 24.9 | 21.98 | 325 | 77 | 23.7 | 20.29 | 0.93 | (0.68,1.27) | 0.6363 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.1500 |
| No | 161 | 33 | 20.5 | 17.47 | 168 | 35 | 20.8 | 17.09 | 0.95 | (0.59,1.53) | 0.8335 | |
| Yes | 1115 | 242 | 21.7 | 18.92 | 1110 | 164 | 14.8 | 12.10 | 0.65 | (0.53,0.79) | <0.0001 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6843 |
| No | 62 | 15 | 24.2 | 21.03 | 72 | 13 | 18.1 | 16.23 | 0.80 | (0.38,1.68) | 0.5533 | |
| Yes | 1214 | 260 | 21.4 | 18.61 | 1206 | 186 | 15.4 | 12.57 | 0.68 | (0.56,0.82) | <0.0001 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3024 |
| No | 46 | 7 | 15.2 | 12.32 | 57 | 3 | 5.3 | 4.21 | 0.34 | (0.09,1.32) | 0.1197 | |
| Yes | 1230 | 268 | 21.8 | 18.99 | 1221 | 196 | 16.1 | 13.16 | 0.70 | (0.58,0.84) | 0.0002 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.3.4: 1**

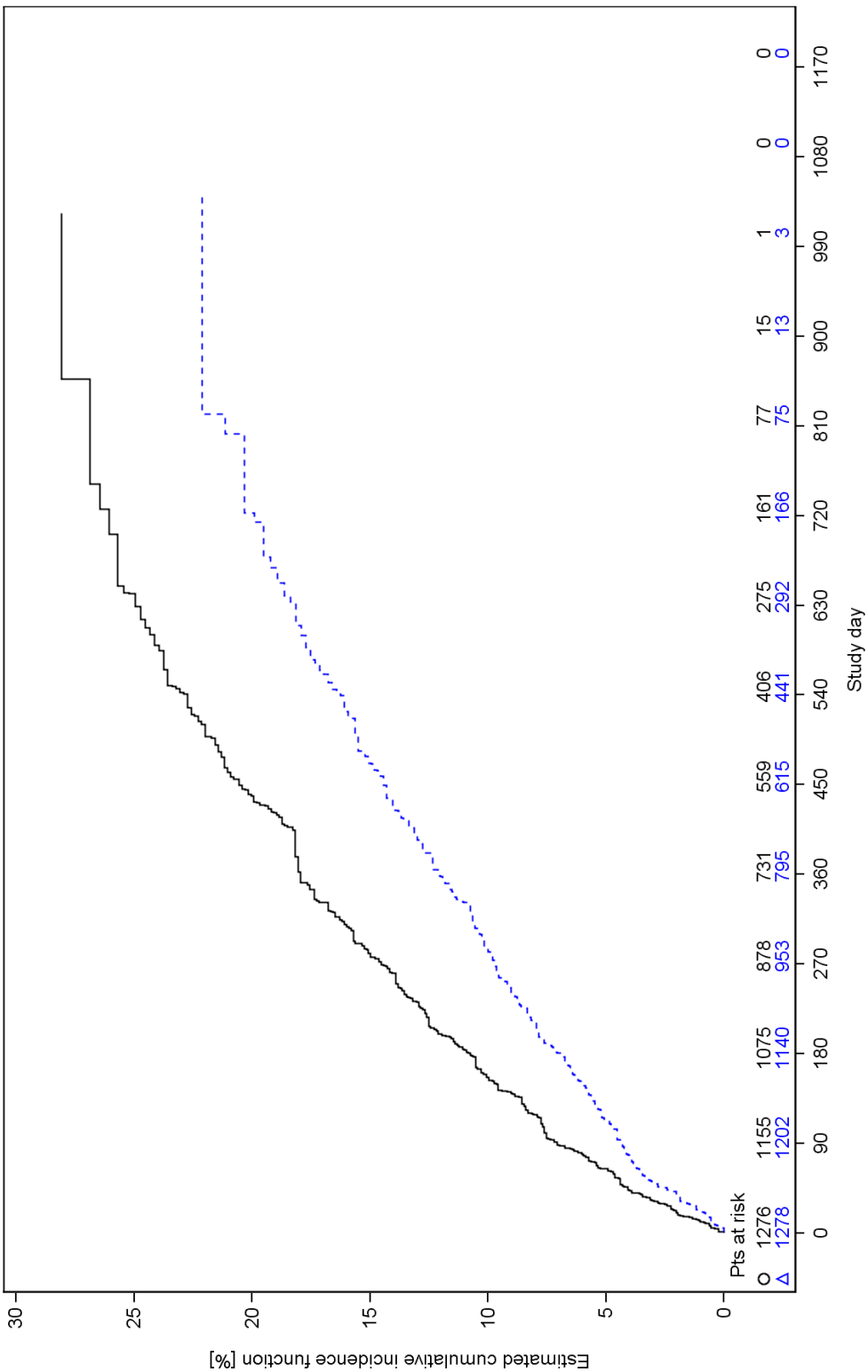


Figure R.3.1.1.3.4: 1 Time to first occurrence of an adjudicated HHF, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.3.4: 2**

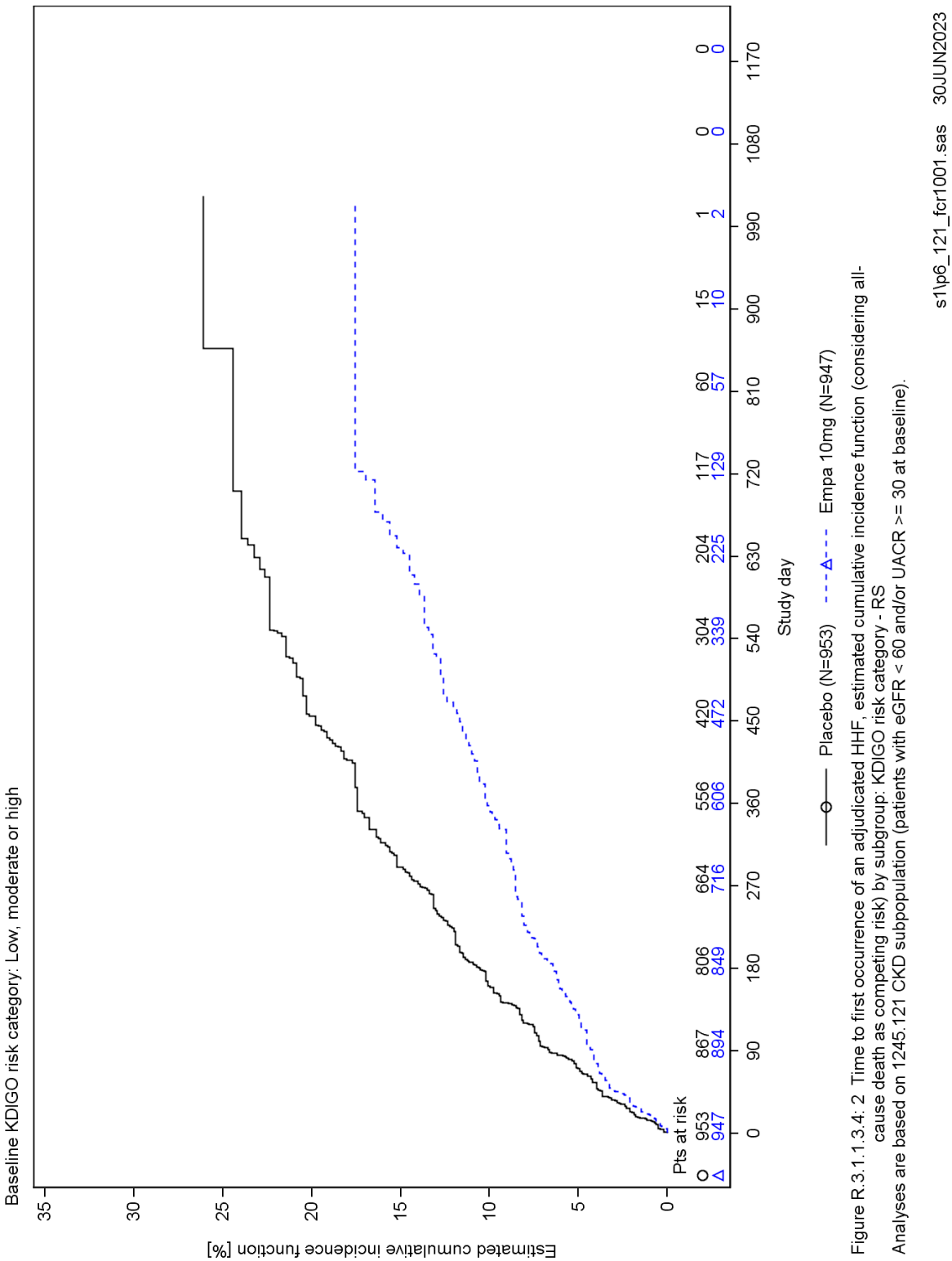


Figure R.3.1.1.3.4: 2 Time to first occurrence of an adjudicated HHF, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: KDIGO risk category - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.3.4: 2**

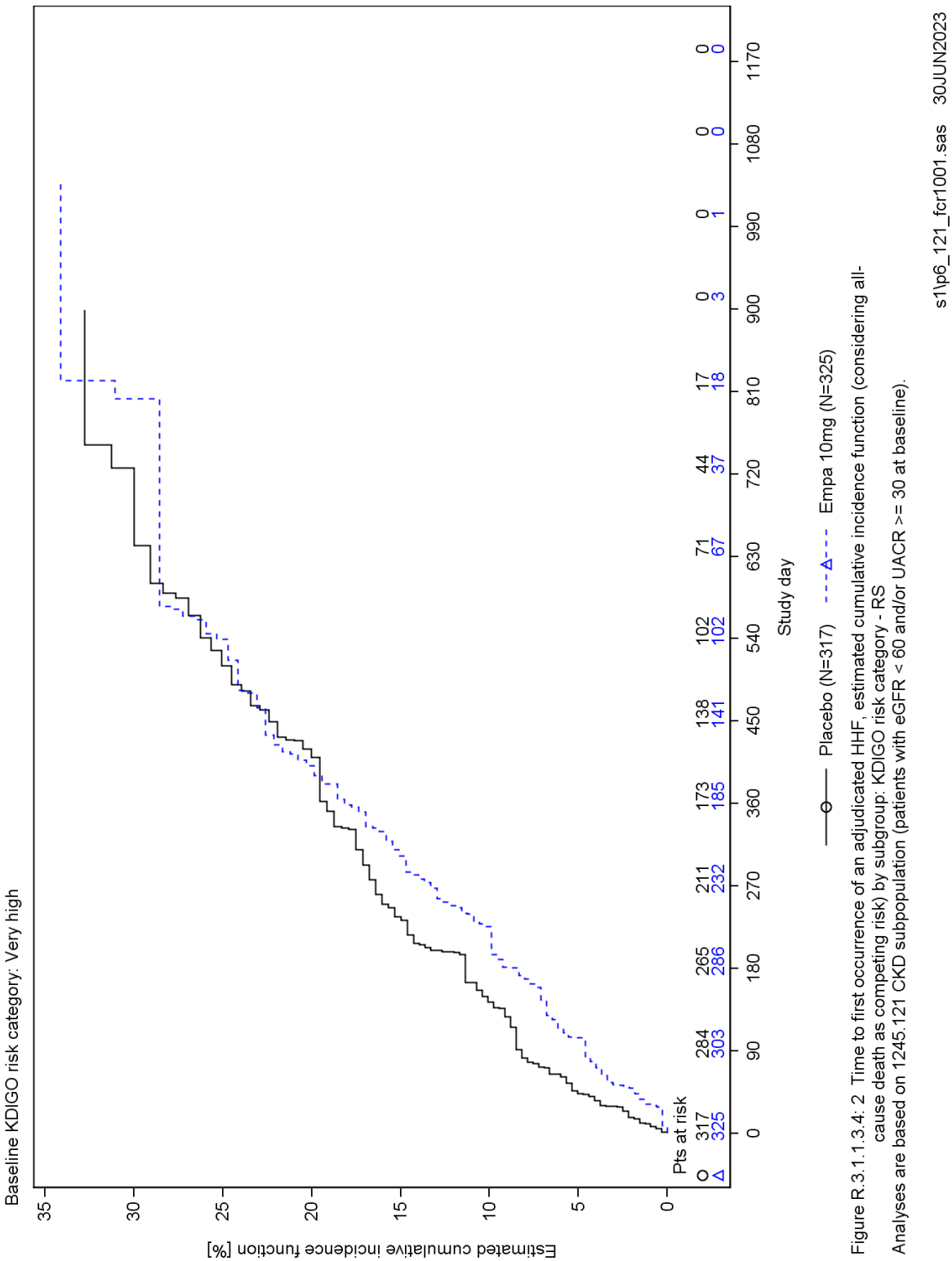


Figure R.3.1.1.3.4: 2 Time to first occurrence of an adjudicated HHF, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: KDIGO risk category - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.3.1.1.3.5 Time to occurrence of adjudicated hospitalization for heart failure (first and recurrent)

Table R.3.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 275 | 21.6 | 443 | 26.40 | 1278 | 199 | 15.6 | 317 | 18.70 | 0.70 | (0.57,0.88) | 0.0016 | |
| Sex | | | | | | | | | | | | | | 0.2886 |
| Male | 959 | 214 | 22.3 | 352 | 27.64 | 975 | 165 | 16.9 | 252 | 19.46 | 0.75 | (0.59,0.96) | 0.0239 | |
| Female | 317 | 61 | 19.2 | 91 | 22.47 | 303 | 34 | 11.2 | 65 | 16.25 | 0.57 | (0.36,0.90) | 0.0163 | |
| Age [years] | | | | | | | | | | | | | | 0.6995 |
| <65 | 436 | 113 | 25.9 | 185 | 32.34 | 392 | 67 | 17.1 | 104 | 20.16 | 0.67 | (0.46,0.97) | 0.0323 | |
| >=65 | 840 | 162 | 19.3 | 258 | 23.32 | 886 | 132 | 14.9 | 213 | 18.06 | 0.73 | (0.56,0.96) | 0.0223 | |
| Region | | | | | | | | | | | | | | 0.2092 |
| North America | 161 | 44 | 27.3 | 76 | 35.48 | 159 | 35 | 22.0 | 73 | 31.03 | 0.73 | (0.42,1.27) | 0.2696 | |
| Latin America | 420 | 84 | 20.0 | 116 | 22.78 | 440 | 57 | 13.0 | 81 | 15.24 | 0.69 | (0.47,1.03) | 0.0672 | |
| Europe | 471 | 84 | 17.8 | 121 | 18.92 | 467 | 77 | 16.5 | 113 | 17.76 | 0.91 | (0.64,1.32) | 0.6316 | |
| Asia | 174 | 56 | 32.2 | 119 | 47.67 | 165 | 26 | 15.8 | 44 | 18.89 | 0.41 | (0.24,0.71) | 0.0014 | |
| Other | 50 | 7 | 14.0 | 11 | 16.77 | 47 | 4 | 8.5 | 6 | 10.16 | 0.59 | (0.16,2.18) | 0.4328 | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8478 |
| Diabetic | 696 | 167 | 24.0 | 277 | 29.88 | 698 | 119 | 17.0 | 190 | 20.72 | 0.69 | (0.52,0.92) | 0.0126 | |
| Non-Diabetic | 580 | 108 | 18.6 | 166 | 22.10 | 580 | 80 | 13.8 | 127 | 16.32 | 0.72 | (0.52,1.01) | 0.0584 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7810 |
| <30 | 890 | 185 | 20.8 | 292 | 24.60 | 836 | 112 | 13.4 | 184 | 16.68 | 0.68 | (0.52,0.89) | 0.0048 | |
| >=30 | 386 | 90 | 23.3 | 151 | 30.73 | 442 | 87 | 19.7 | 133 | 22.46 | 0.72 | (0.50,1.04) | 0.0826 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5856 |
| <130 | 859 | 205 | 23.9 | 314 | 28.15 | 834 | 145 | 17.4 | 223 | 20.54 | 0.74 | (0.57,0.96) | 0.0251 | |
| >=130 | 417 | 70 | 16.8 | 129 | 22.92 | 444 | 54 | 12.2 | 94 | 15.42 | 0.65 | (0.44,0.95) | 0.0271 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1497 |
| <75 | 720 | 151 | 21.0 | 233 | 24.70 | 678 | 112 | 16.5 | 184 | 20.88 | 0.85 | (0.64,1.14) | 0.2805 | |
| 75 to <85 | 348 | 79 | 22.7 | 132 | 28.63 | 382 | 60 | 15.7 | 93 | 18.12 | 0.58 | (0.38,0.86) | 0.0076 | |
| >=85 | 208 | 45 | 21.6 | 78 | 28.48 | 218 | 27 | 12.4 | 40 | 13.29 | 0.52 | (0.30,0.89) | 0.0181 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline diabetes status, baseline LVEF, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.3.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1414 |
| <30 | 90 | 24 | 26.7 | 42 | 40.36 | 115 | 28 | 24.3 | 41 | 26.76 | 0.59 | (0.29,1.20) | 0.1451 | |
| 30 to <45 | 349 | 68 | 19.5 | 109 | 23.49 | 345 | 62 | 18.0 | 102 | 22.37 | 0.99 | (0.66,1.49) | 0.9700 | |
| >=45 | 837 | 183 | 21.9 | 292 | 26.30 | 818 | 109 | 13.3 | 174 | 16.02 | 0.61 | (0.47,0.81) | 0.0005 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4825 |
| Normal (<30) | 452 | 67 | 14.8 | 99 | 16.78 | 456 | 52 | 11.4 | 84 | 13.45 | 0.78 | (0.53,1.15) | 0.2085 | |
| Microalbuminuria (30 to <=300) | 628 | 145 | 23.1 | 232 | 28.07 | 608 | 105 | 17.3 | 173 | 21.68 | 0.74 | (0.55,1.00) | 0.0538 | |
| Macroalbuminuria (>300) | 189 | 60 | 31.7 | 108 | 42.69 | 207 | 42 | 20.3 | 60 | 22.62 | 0.54 | (0.32,0.89) | 0.0165 | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2813 |
| Low, moderate or high | 953 | 193 | 20.3 | 306 | 24.46 | 947 | 122 | 12.9 | 202 | 16.05 | 0.66 | (0.51,0.85) | 0.0017 | |
| Very high | 317 | 79 | 24.9 | 133 | 31.66 | 325 | 77 | 23.7 | 115 | 26.69 | 0.86 | (0.57,1.29) | 0.4588 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2501 |
| No | 161 | 33 | 20.5 | 58 | 26.56 | 168 | 35 | 20.8 | 64 | 27.60 | 0.96 | (0.53,1.72) | 0.8904 | |
| Yes | 1115 | 242 | 21.7 | 385 | 26.37 | 1110 | 164 | 14.8 | 253 | 17.29 | 0.66 | (0.53,0.84) | 0.0006 | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6593 |
| No | 62 | 15 | 24.2 | 33 | 40.44 | 72 | 13 | 18.1 | 20 | 22.33 | 0.57 | (0.23,1.43) | 0.2319 | |
| Yes | 1214 | 260 | 21.4 | 410 | 25.68 | 1206 | 186 | 15.4 | 297 | 18.50 | 0.71 | (0.57,0.89) | 0.0027 | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4446 |
| No | 46 | 7 | 15.2 | 12 | 19.34 | 57 | 3 | 5.3 | 5 | 6.61 | 0.42 | (0.11,1.59) | 0.2032 | |
| Yes | 1230 | 268 | 21.8 | 431 | 26.67 | 1221 | 196 | 16.1 | 312 | 19.26 | 0.71 | (0.57,0.89) | 0.0028 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline diabetes status, baseline LVEF, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.3.5: 1**

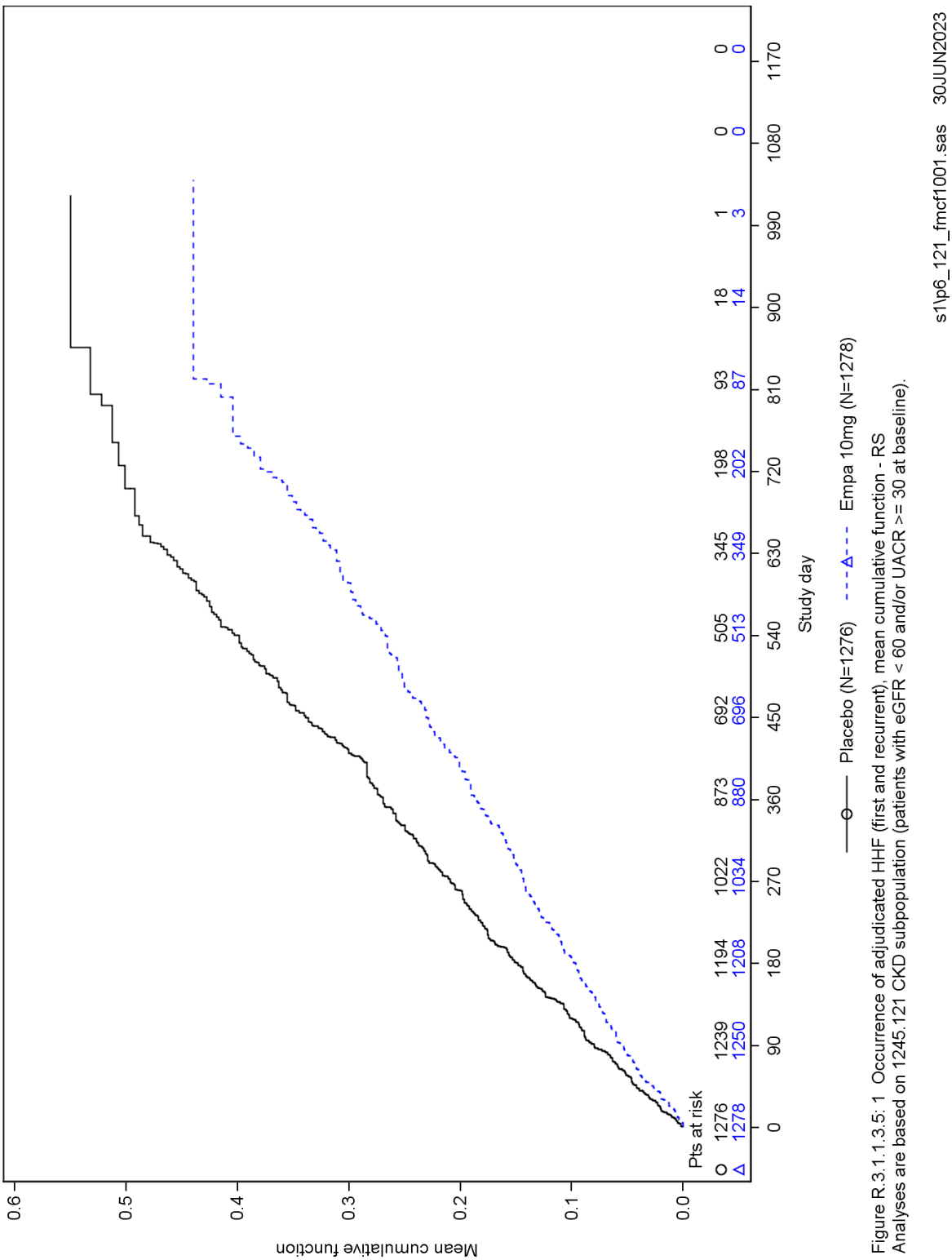


Figure R.3.1.1.3.5: 1 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.3.1.1.3.6 Time to first occurrence of all-cause hospitalization

Table R.3.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 589 | 46.2 | 48.85 | 1278 | 528 | 41.3 | 40.72 | 0.84 | (0.75,0.94) | 0.0036 | |
| Sex | | | | | | | | | | | | 0.4112 |
| Male | 959 | 460 | 48.0 | 50.73 | 975 | 422 | 43.3 | 43.48 | 0.86 | (0.75,0.98) | 0.0269 | |
| Female | 317 | 129 | 40.7 | 43.13 | 303 | 106 | 35.0 | 32.52 | 0.76 | (0.59,0.99) | 0.0391 | |
| Age [years] | | | | | | | | | | | | 0.9437 |
| <65 | 436 | 197 | 45.2 | 48.70 | 392 | 156 | 39.8 | 39.93 | 0.84 | (0.68,1.03) | 0.0967 | |
| >=65 | 840 | 392 | 46.7 | 48.92 | 886 | 372 | 42.0 | 41.07 | 0.84 | (0.73,0.97) | 0.0195 | |
| Region | | | | | | | | | | | | 0.1303 |
| North America | 161 | 93 | 57.8 | 68.56 | 159 | 83 | 52.2 | 52.15 | 0.79 | (0.59,1.07) | 0.1279 | |
| Latin America | 420 | 173 | 41.2 | 45.00 | 440 | 156 | 35.5 | 35.40 | 0.79 | (0.63,0.98) | 0.0306 | |
| Europe | 471 | 214 | 45.4 | 45.79 | 467 | 213 | 45.6 | 46.42 | 1.01 | (0.83,1.22) | 0.9282 | |
| Asia | 174 | 92 | 52.9 | 55.90 | 165 | 65 | 39.4 | 35.35 | 0.65 | (0.47,0.89) | 0.0076 | |
| Other | 50 | 17 | 34.0 | 31.61 | 47 | 11 | 23.4 | 20.40 | 0.64 | (0.30,1.36) | 0.2445 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.4171 |
| Diabetic | 696 | 326 | 46.8 | 49.45 | 698 | 302 | 43.3 | 42.87 | 0.88 | (0.75,1.02) | 0.0968 | |
| Non-Diabetic | 580 | 263 | 45.3 | 48.12 | 580 | 226 | 39.0 | 38.18 | 0.79 | (0.66,0.95) | 0.0110 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.8735 |
| <30 | 890 | 402 | 45.2 | 46.25 | 836 | 329 | 39.4 | 38.37 | 0.83 | (0.71,0.96) | 0.0101 | |
| >=30 | 386 | 187 | 48.4 | 55.57 | 442 | 199 | 45.0 | 45.31 | 0.84 | (0.69,1.03) | 0.0930 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.9236 |
| <130 | 859 | 411 | 47.8 | 51.67 | 834 | 359 | 43.0 | 44.14 | 0.85 | (0.73,0.98) | 0.0211 | |
| >=130 | 417 | 178 | 42.7 | 43.37 | 444 | 169 | 38.1 | 34.98 | 0.84 | (0.68,1.03) | 0.0957 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.0692 |
| <75 | 720 | 334 | 46.4 | 48.39 | 678 | 307 | 45.3 | 46.56 | 0.95 | (0.81,1.11) | 0.4969 | |
| 75 to <85 | 348 | 153 | 44.0 | 46.84 | 382 | 139 | 36.4 | 34.71 | 0.75 | (0.59,0.94) | 0.0133 | |
| >=85 | 208 | 102 | 49.0 | 53.99 | 218 | 82 | 37.6 | 34.64 | 0.68 | (0.51,0.91) | 0.0093 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.3.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.3427 |
| <30 | 90 | 48 | 53.3 | 70.81 | 115 | 72 | 62.6 | 68.37 | 1.01 | (0.70,1.46) | 0.9620 | |
| 30 to <45 | 349 | 160 | 45.8 | 47.63 | 345 | 146 | 42.3 | 42.34 | 0.89 | (0.71,1.11) | 0.2965 | |
| >=45 | 837 | 381 | 45.5 | 47.50 | 818 | 310 | 37.9 | 36.63 | 0.78 | (0.67,0.90) | 0.0010 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2812 |
| Normal (<30) | 452 | 192 | 42.5 | 43.38 | 456 | 174 | 38.2 | 35.89 | 0.83 | (0.67,1.01) | 0.0685 | |
| Microalbuminuria (30 to <=300) | 628 | 286 | 45.5 | 47.17 | 608 | 255 | 41.9 | 41.69 | 0.90 | (0.76,1.07) | 0.2481 | |
| Macroalbuminuria (>300) | 189 | 107 | 56.6 | 70.66 | 207 | 98 | 47.3 | 50.52 | 0.70 | (0.53,0.92) | 0.0100 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.1338 |
| Low, moderate or high | 953 | 427 | 44.8 | 46.48 | 947 | 360 | 38.0 | 36.73 | 0.80 | (0.69,0.92) | 0.0014 | |
| Very high | 317 | 159 | 50.2 | 56.16 | 325 | 168 | 51.7 | 54.13 | 0.97 | (0.78,1.21) | 0.7822 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.3485 |
| No | 161 | 77 | 47.8 | 48.68 | 168 | 82 | 48.8 | 50.26 | 0.96 | (0.71,1.32) | 0.8163 | |
| Yes | 1115 | 512 | 45.9 | 48.87 | 1110 | 446 | 40.2 | 39.35 | 0.82 | (0.72,0.93) | 0.0023 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.8494 |
| No | 62 | 35 | 56.5 | 62.43 | 72 | 33 | 45.8 | 50.03 | 0.80 | (0.50,1.29) | 0.3632 | |
| Yes | 1214 | 554 | 45.6 | 48.18 | 1206 | 495 | 41.0 | 40.23 | 0.84 | (0.74,0.95) | 0.0050 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.0331 |
| No | 46 | 22 | 47.8 | 53.33 | 57 | 14 | 24.6 | 22.00 | 0.41 | (0.21,0.80) | 0.0094 | |
| Yes | 1230 | 567 | 46.1 | 48.69 | 1221 | 514 | 42.1 | 41.69 | 0.86 | (0.77,0.97) | 0.0153 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, baseline LVEF, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.3.6: 1**

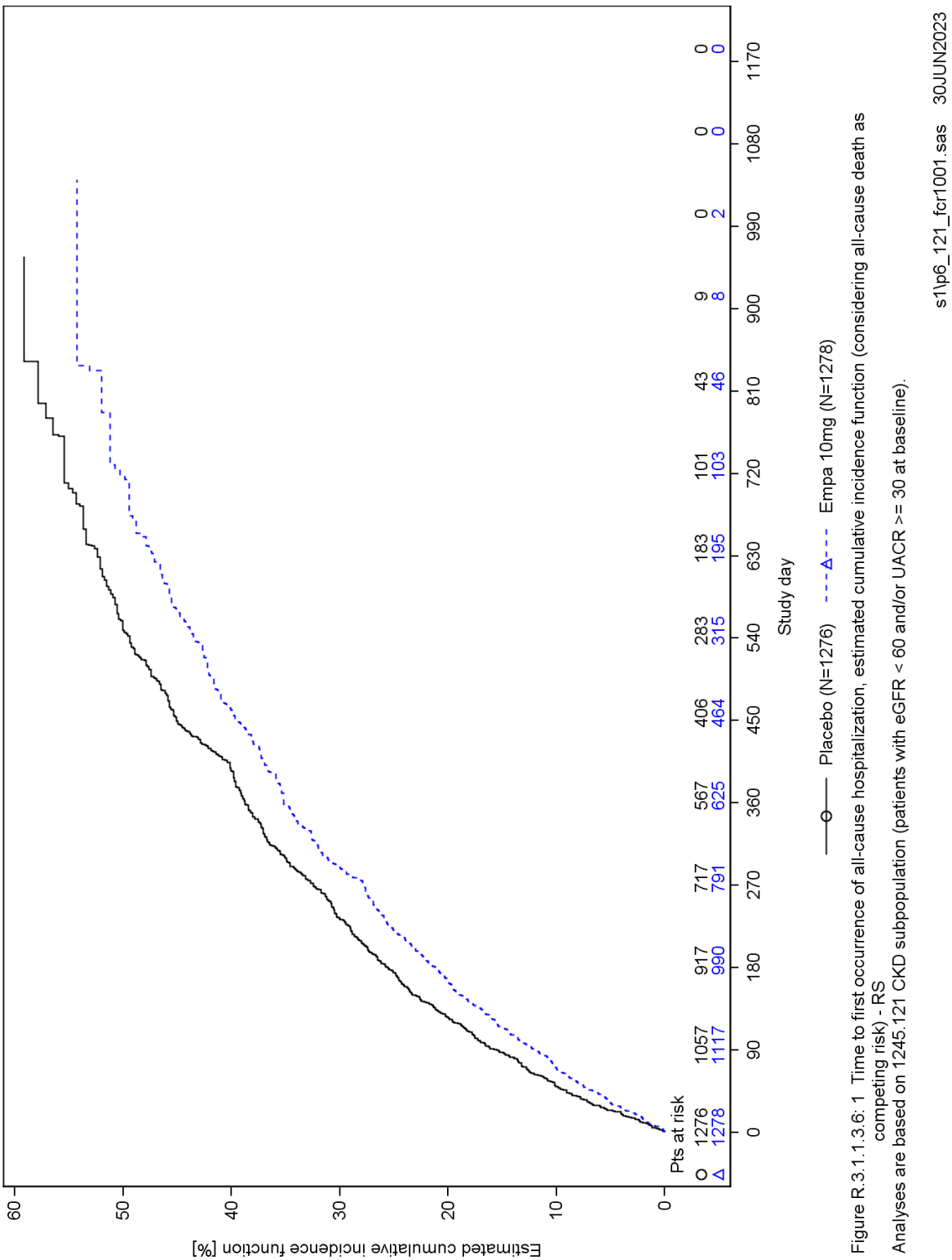


Figure R.3.1.1.3.6: 1 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.3.6: 2**

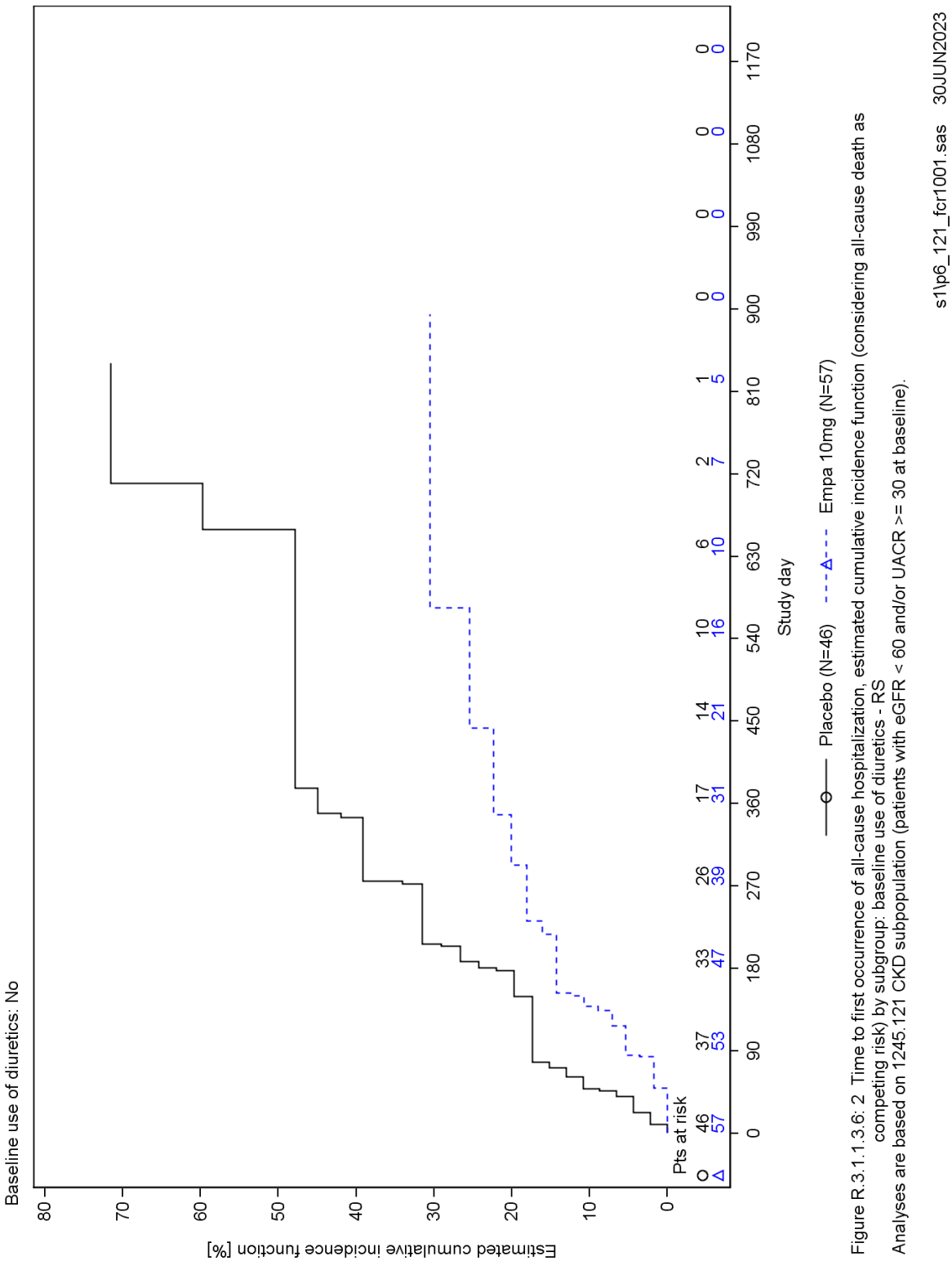


Figure R.3.1.1.3.6: 2 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline use of diuretics - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.3.6: 2**

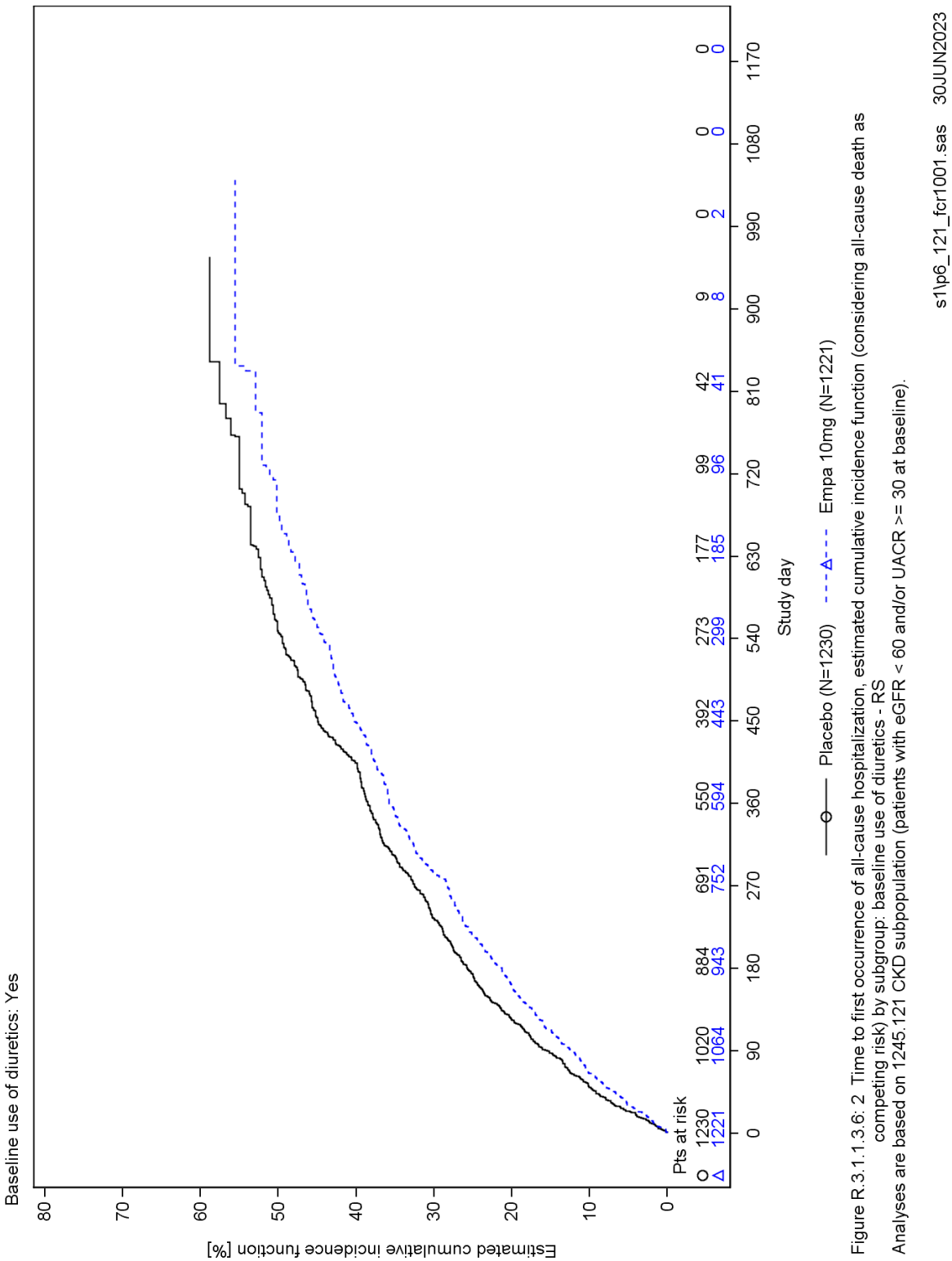


Figure R.3.1.1.3.6: 2 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline use of diuretics - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.3.1.1.3.7 Time to occurrence of all-cause hospitalizations (first and recurrent)

Table R.3.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1276 | 589 | 46.2 | 1188 | 70.79 | 1278 | 528 | 41.3 | 1064 | 62.76 | 0.85 | (0.74,0.98) | 0.0265 | |
| Sex | | | | | | | | | | | | | | 0.4737 |
| Male | 959 | 460 | 48.0 | 932 | 73.20 | 975 | 422 | 43.3 | 834 | 64.39 | 0.88 | (0.75,1.03) | 0.1123 | |
| Female | 317 | 129 | 40.7 | 256 | 63.21 | 303 | 106 | 35.0 | 230 | 57.48 | 0.78 | (0.58,1.04) | 0.0920 | |
| Age [years] | | | | | | | | | | | | | | 0.6184 |
| <65 | 436 | 197 | 45.2 | 425 | 74.29 | 392 | 156 | 39.8 | 343 | 66.48 | 0.90 | (0.70,1.15) | 0.3860 | |
| >=65 | 840 | 392 | 46.7 | 763 | 68.97 | 886 | 372 | 42.0 | 721 | 61.13 | 0.83 | (0.70,0.99) | 0.0351 | |
| Region | | | | | | | | | | | | | | 0.2033 |
| North America | 161 | 93 | 57.8 | 214 | 99.90 | 159 | 83 | 52.2 | 224 | 95.23 | 0.83 | (0.58,1.20) | 0.3265 | |
| Latin America | 420 | 173 | 41.2 | 288 | 56.56 | 440 | 156 | 35.5 | 239 | 44.95 | 0.82 | (0.63,1.06) | 0.1333 | |
| Europe | 471 | 214 | 45.4 | 431 | 67.38 | 467 | 213 | 45.6 | 454 | 71.33 | 1.01 | (0.80,1.27) | 0.9422 | |
| Asia | 174 | 92 | 52.9 | 225 | 90.13 | 165 | 65 | 39.4 | 130 | 55.80 | 0.61 | (0.42,0.89) | 0.0110 | |
| Other | 50 | 17 | 34.0 | 30 | 45.73 | 47 | 11 | 23.4 | 17 | 28.77 | 0.58 | (0.25,1.34) | 0.2035 | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2667 |
| Diabetic | 696 | 326 | 46.8 | 688 | 74.20 | 698 | 302 | 43.3 | 610 | 66.51 | 0.92 | (0.76,1.11) | 0.3669 | |
| Non-Diabetic | 580 | 263 | 45.3 | 500 | 66.57 | 580 | 226 | 39.0 | 454 | 58.34 | 0.78 | (0.63,0.96) | 0.0220 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7377 |
| <30 | 890 | 402 | 45.2 | 778 | 65.55 | 836 | 329 | 39.4 | 665 | 60.28 | 0.86 | (0.73,1.03) | 0.0968 | |
| >=30 | 386 | 187 | 48.4 | 410 | 83.44 | 442 | 199 | 45.0 | 399 | 67.37 | 0.82 | (0.64,1.05) | 0.1124 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8005 |
| <130 | 859 | 411 | 47.8 | 827 | 74.13 | 834 | 359 | 43.0 | 727 | 66.95 | 0.87 | (0.73,1.03) | 0.1032 | |
| >=130 | 417 | 178 | 42.7 | 361 | 64.15 | 444 | 169 | 38.1 | 337 | 55.29 | 0.83 | (0.65,1.06) | 0.1439 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2722 |
| <75 | 720 | 334 | 46.4 | 676 | 71.66 | 678 | 307 | 45.3 | 623 | 70.68 | 0.94 | (0.78,1.14) | 0.5503 | |
| 75 to <85 | 348 | 153 | 44.0 | 309 | 67.02 | 382 | 139 | 36.4 | 280 | 54.57 | 0.75 | (0.57,0.99) | 0.0387 | |
| >=85 | 208 | 102 | 49.0 | 203 | 74.12 | 218 | 82 | 37.6 | 161 | 53.51 | 0.74 | (0.53,1.04) | 0.0865 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline diabetes status, baseline LVEF, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.3.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3747 |
| <30 | 90 | 48 | 53.3 | 111 | 106.66 | 115 | 72 | 62.6 | 143 | 93.32 | 0.86 | (0.54,1.38) | 0.5348 | |
| 30 to <45 | 349 | 160 | 45.8 | 329 | 70.91 | 345 | 146 | 42.3 | 311 | 68.19 | 0.99 | (0.76,1.29) | 0.9478 | |
| >=45 | 837 | 381 | 45.5 | 748 | 67.37 | 818 | 310 | 37.9 | 610 | 56.17 | 0.79 | (0.66,0.94) | 0.0090 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8732 |
| Normal (<30) | 452 | 192 | 42.5 | 358 | 60.69 | 456 | 174 | 38.2 | 350 | 56.03 | 0.88 | (0.70,1.12) | 0.3144 | |
| Microalbuminuria (30 to <=300) | 628 | 286 | 45.5 | 584 | 70.66 | 608 | 255 | 41.9 | 524 | 65.68 | 0.86 | (0.70,1.05) | 0.1423 | |
| Macroalbuminuria (>300) | 189 | 107 | 56.6 | 235 | 92.89 | 207 | 98 | 47.3 | 186 | 70.13 | 0.79 | (0.56,1.12) | 0.1844 | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3897 |
| Low, moderate or high | 953 | 427 | 44.8 | 830 | 66.35 | 947 | 360 | 38.0 | 720 | 57.21 | 0.83 | (0.70,0.98) | 0.0273 | |
| Very high | 317 | 159 | 50.2 | 351 | 83.56 | 325 | 168 | 51.7 | 344 | 79.84 | 0.95 | (0.73,1.25) | 0.7256 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4101 |
| No | 161 | 77 | 47.8 | 155 | 70.98 | 168 | 82 | 48.8 | 183 | 78.93 | 0.99 | (0.67,1.45) | 0.9489 | |
| Yes | 1115 | 512 | 45.9 | 1033 | 70.76 | 1110 | 446 | 40.2 | 881 | 60.20 | 0.83 | (0.71,0.97) | 0.0157 | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1430 |
| No | 62 | 35 | 56.5 | 86 | 105.38 | 72 | 33 | 45.8 | 57 | 63.63 | 0.55 | (0.30,1.00) | 0.0517 | |
| Yes | 1214 | 554 | 45.6 | 1102 | 69.02 | 1206 | 495 | 41.0 | 1007 | 62.71 | 0.87 | (0.75,1.01) | 0.0643 | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.0831 |
| No | 46 | 22 | 47.8 | 40 | 64.45 | 57 | 14 | 24.6 | 21 | 27.78 | 0.43 | (0.20,0.94) | 0.0351 | |
| Yes | 1230 | 567 | 46.1 | 1148 | 71.03 | 1221 | 514 | 42.1 | 1043 | 64.39 | 0.87 | (0.75,1.00) | 0.0574 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline diabetes status, baseline LVEF, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.3.1.1.3.7: 1**

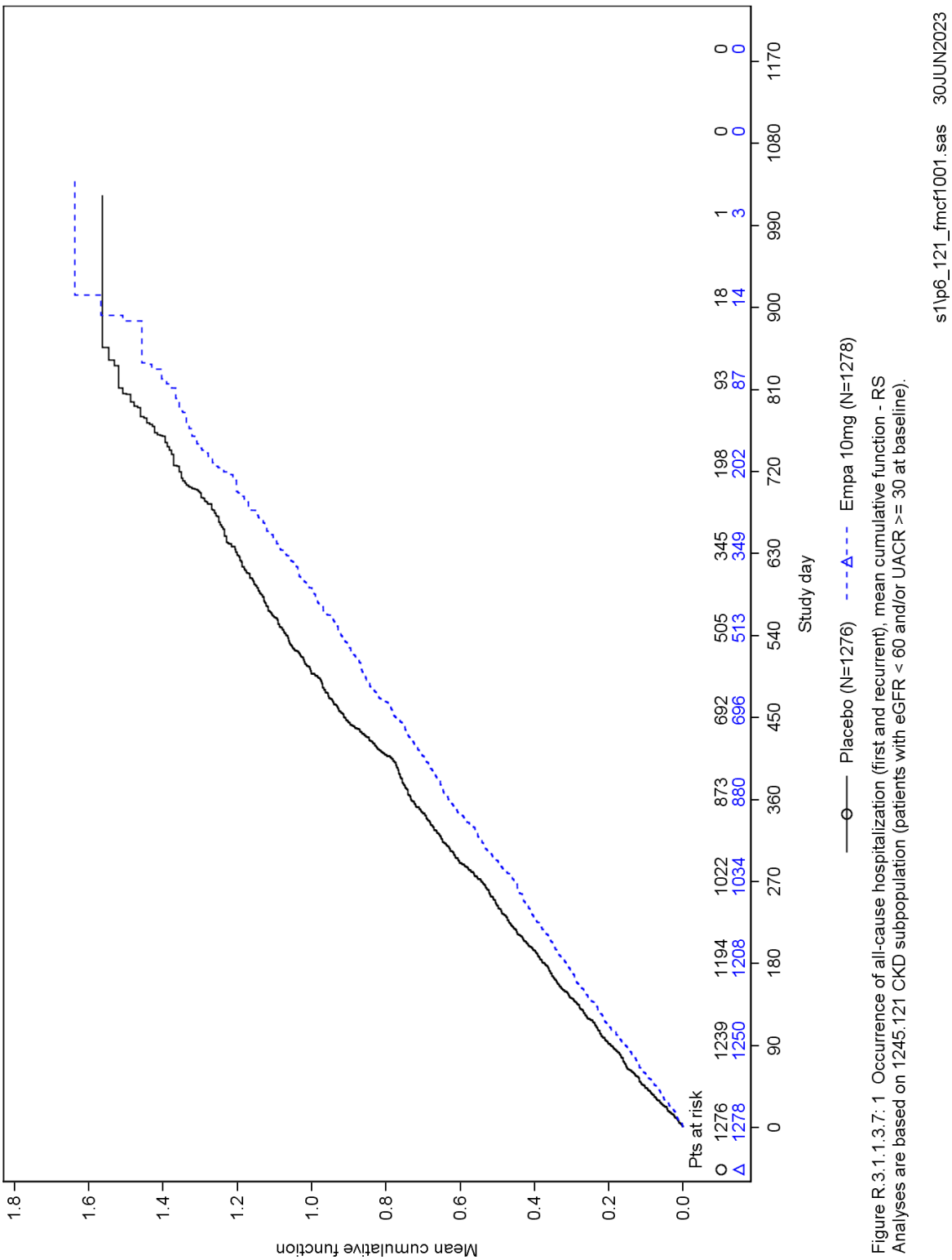


Figure R.3.1.1.3.7: 1 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function - RS
Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.3.1.2**

R.3.1.2.1 Responder analyses based on last value during planned treatment period

**R.3.1.2.1.1**

R.3.1.2.1.1 EQ-VAS responder analysis (15 points)

Table R.3.1.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1196 | 177 | 14.8 | 1215 | 188 | 15.5 | 1.06 | (0.88,1.27) | 0.5354 | 1.08 | (0.86,1.37) | |
| Sex | | | | | | | | | | | | 0.9964 |
| Male | 906 | 129 | 14.2 | 931 | 136 | 14.6 | 1.06 | (0.85,1.31) | 0.6004 | 1.08 | (0.82,1.42) | |
| Female | 290 | 48 | 16.6 | 284 | 52 | 18.3 | 1.06 | (0.75,1.48) | 0.7436 | 1.10 | (0.70,1.73) | |
| Age [years] | | | | | | | | | | | | 0.7963 |
| <65 | 412 | 46 | 11.2 | 374 | 41 | 11.0 | 1.01 | (0.69,1.49) | 0.9598 | 1.01 | (0.64,1.62) | |
| >=65 | 784 | 131 | 16.7 | 841 | 147 | 17.5 | 1.07 | (0.87,1.31) | 0.5167 | 1.10 | (0.84,1.45) | |
| Region | | | | | | | | | | | | 0.6426 |
| North America | 144 | 22 | 15.3 | 155 | 24 | 15.5 | 1.08 | (0.64,1.82) | 0.7679 | 1.11 | (0.57,2.14) | |
| Latin America | 392 | 44 | 11.2 | 408 | 53 | 13.0 | 1.19 | (0.83,1.71) | 0.3477 | 1.23 | (0.79,1.93) | |
| Europe | 445 | 77 | 17.3 | 447 | 82 | 18.3 | 1.04 | (0.80,1.37) | 0.7569 | 1.07 | (0.75,1.54) | |
| Asia | 170 | 28 | 16.5 | 162 | 28 | 17.3 | 1.03 | (0.65,1.61) | 0.9073 | 1.05 | (0.58,1.92) | |
| Other | 45 | 6 | 13.3 | 43 | 1 | 2.3 | 0.23 | (0.03,1.84) | 0.1648 | 0.20 | (0.02,1.79) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.0436 |
| Diabetic | 652 | 93 | 14.3 | 662 | 113 | 17.1 | 1.25 | (0.98,1.59) | 0.0705 | 1.34 | (0.98,1.84) | |
| Non-Diabetic | 544 | 84 | 15.4 | 553 | 75 | 13.6 | 0.86 | (0.65,1.13) | 0.2686 | 0.83 | (0.58,1.18) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.3216 |
| <30 | 839 | 125 | 14.9 | 795 | 120 | 15.1 | 0.99 | (0.79,1.23) | 0.9097 | 0.99 | (0.74,1.32) | |
| >=30 | 357 | 52 | 14.6 | 420 | 68 | 16.2 | 1.20 | (0.87,1.66) | 0.2607 | 1.28 | (0.85,1.94) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3626 |
| <130 | 799 | 127 | 15.9 | 785 | 125 | 15.9 | 1.00 | (0.81,1.24) | 0.9703 | 1.01 | (0.76,1.35) | |
| >=130 | 397 | 50 | 12.6 | 430 | 63 | 14.7 | 1.21 | (0.87,1.68) | 0.2675 | 1.28 | (0.84,1.94) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.8919 |
| <75 | 672 | 122 | 18.2 | 641 | 118 | 18.4 | 1.04 | (0.84,1.30) | 0.7069 | 1.07 | (0.80,1.44) | |
| 75 to <85 | 323 | 36 | 11.1 | 361 | 46 | 12.7 | 1.13 | (0.76,1.67) | 0.5363 | 1.16 | (0.72,1.88) | |
| >=85 | 201 | 19 | 9.5 | 213 | 24 | 11.3 | 1.17 | (0.66,2.07) | 0.5843 | 1.21 | (0.63,2.34) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.7330 |
| <30 | 80 | 14 | 17.5 | 107 | 22 | 20.6 | 1.28 | (0.71,2.30) | 0.4041 | 1.38 | (0.63,3.05) | |
| 30 to <45 | 335 | 55 | 16.4 | 332 | 64 | 19.3 | 1.09 | (0.80,1.48) | 0.5962 | 1.14 | (0.75,1.73) | |
| >=45 | 781 | 108 | 13.8 | 776 | 102 | 13.1 | 1.00 | (0.79,1.28) | 0.9680 | 1.01 | (0.75,1.37) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7935 |
| Normal (<30) | 431 | 79 | 18.3 | 440 | 80 | 18.2 | 0.99 | (0.76,1.30) | 0.9583 | 1.00 | (0.70,1.43) | |
| Microalbuminuria (30 to <=300) | 579 | 82 | 14.2 | 569 | 88 | 15.5 | 1.12 | (0.86,1.46) | 0.3992 | 1.17 | (0.83,1.65) | |
| Macroalbuminuria (>300) | 181 | 15 | 8.3 | 200 | 19 | 9.5 | 1.15 | (0.61,2.17) | 0.6600 | 1.17 | (0.56,2.45) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4553 |
| Low, moderate or high | 892 | 130 | 14.6 | 902 | 132 | 14.6 | 1.02 | (0.83,1.27) | 0.8311 | 1.04 | (0.79,1.36) | |
| Very high | 299 | 46 | 15.4 | 308 | 56 | 18.2 | 1.19 | (0.85,1.68) | 0.3081 | 1.27 | (0.81,1.99) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.2865 |
| No | 152 | 27 | 17.8 | 159 | 25 | 15.7 | 0.83 | (0.52,1.33) | 0.4459 | 0.80 | (0.42,1.50) | |
| Yes | 1044 | 150 | 14.4 | 1056 | 163 | 15.4 | 1.10 | (0.90,1.34) | 0.3465 | 1.14 | (0.88,1.46) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6117 |
| No | 57 | 4 | 7.0 | 66 | 6 | 9.1 | 1.42 | (0.45,4.53) | 0.5492 | 1.51 | (0.39,5.83) | |
| Yes | 1139 | 173 | 15.2 | 1149 | 182 | 15.8 | 1.05 | (0.88,1.26) | 0.5907 | 1.07 | (0.85,1.36) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2542 |
| No | 43 | 7 | 16.3 | 54 | 5 | 9.3 | 0.59 | (0.21,1.65) | 0.3137 | 0.54 | (0.15,1.94) | |
| Yes | 1153 | 170 | 14.7 | 1161 | 183 | 15.8 | 1.08 | (0.90,1.30) | 0.3981 | 1.11 | (0.88,1.41) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1196 | 301 | 25.2 | 1215 | 334 | 27.5 | 1.05 | (0.93,1.19) | 0.4347 | 1.10 | (0.89,1.37) | |
| Sex | | | | | | | | | | | | 0.9565 |
| Male | 906 | 227 | 25.1 | 931 | 255 | 27.4 | 1.05 | (0.91,1.21) | 0.4833 | 1.09 | (0.85,1.39) | |
| Female | 290 | 74 | 25.5 | 284 | 79 | 27.8 | 1.04 | (0.82,1.33) | 0.7312 | 1.16 | (0.74,1.80) | |
| Age [years] | | | | | | | | | | | | 0.8496 |
| <65 | 412 | 117 | 28.4 | 374 | 123 | 32.9 | 1.07 | (0.87,1.30) | 0.5298 | 1.14 | (0.79,1.64) | |
| >=65 | 784 | 184 | 23.5 | 841 | 211 | 25.1 | 1.04 | (0.89,1.22) | 0.6259 | 1.09 | (0.83,1.41) | |
| Region | | | | | | | | | | | | 0.5988 |
| North America | 144 | 25 | 17.4 | 155 | 45 | 29.0 | 1.40 | (0.92,2.12) | 0.1167 | 2.08 | (1.08,4.01) | |
| Latin America | 392 | 127 | 32.4 | 408 | 137 | 33.6 | 1.06 | (0.89,1.27) | 0.4937 | 1.11 | (0.78,1.58) | |
| Europe | 445 | 96 | 21.6 | 447 | 96 | 21.5 | 1.00 | (0.78,1.27) | 0.9729 | 0.99 | (0.69,1.42) | |
| Asia | 170 | 36 | 21.2 | 162 | 36 | 22.2 | 0.96 | (0.67,1.36) | 0.8047 | 0.89 | (0.50,1.62) | |
| Other | 45 | 17 | 37.8 | 43 | 20 | 46.5 | 0.90 | (0.58,1.39) | 0.6232 | 0.95 | (0.37,2.47) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9017 |
| Diabetic | 652 | 177 | 27.1 | 662 | 197 | 29.8 | 1.06 | (0.90,1.24) | 0.5054 | 1.10 | (0.83,1.46) | |
| Non-Diabetic | 544 | 124 | 22.8 | 553 | 137 | 24.8 | 1.04 | (0.86,1.26) | 0.6951 | 1.12 | (0.81,1.55) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.6980 |
| <30 | 839 | 214 | 25.5 | 795 | 207 | 26.0 | 1.04 | (0.89,1.21) | 0.6214 | 1.07 | (0.83,1.39) | |
| >=30 | 357 | 87 | 24.4 | 420 | 127 | 30.2 | 1.09 | (0.88,1.35) | 0.4102 | 1.21 | (0.83,1.76) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.4896 |
| <130 | 799 | 201 | 25.2 | 785 | 222 | 28.3 | 1.08 | (0.93,1.26) | 0.2999 | 1.16 | (0.89,1.51) | |
| >=130 | 397 | 100 | 25.2 | 430 | 112 | 26.0 | 0.99 | (0.80,1.22) | 0.9072 | 1.00 | (0.69,1.44) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7262 |
| <75 | 672 | 161 | 24.0 | 641 | 173 | 27.0 | 1.10 | (0.93,1.31) | 0.2764 | 1.17 | (0.87,1.56) | |
| 75 to <85 | 323 | 89 | 27.6 | 361 | 103 | 28.5 | 1.01 | (0.82,1.25) | 0.8910 | 1.07 | (0.72,1.60) | |
| >=85 | 201 | 51 | 25.4 | 213 | 58 | 27.2 | 0.97 | (0.72,1.31) | 0.8529 | 0.98 | (0.59,1.65) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4831 |
| <30 | 80 | 20 | 25.0 | 107 | 32 | 29.9 | 1.24 | (0.79,1.93) | 0.3486 | 1.44 | (0.67,3.11) | |
| 30 to <45 | 335 | 83 | 24.8 | 332 | 74 | 22.3 | 0.94 | (0.73,1.20) | 0.5998 | 0.93 | (0.61,1.41) | |
| >=45 | 781 | 198 | 25.4 | 776 | 228 | 29.4 | 1.08 | (0.93,1.25) | 0.3227 | 1.14 | (0.88,1.49) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.3042 |
| Normal (<30) | 431 | 103 | 23.9 | 440 | 99 | 22.5 | 0.92 | (0.73,1.16) | 0.4732 | 0.91 | (0.63,1.30) | |
| Microalbuminuria (30 to <=300) | 579 | 135 | 23.3 | 569 | 166 | 29.2 | 1.15 | (0.97,1.37) | 0.1126 | 1.31 | (0.96,1.79) | |
| Macroalbuminuria (>300) | 181 | 60 | 33.1 | 200 | 66 | 33.0 | 1.04 | (0.81,1.34) | 0.7475 | 1.03 | (0.61,1.72) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.9802 |
| Low, moderate or high | 892 | 216 | 24.2 | 902 | 249 | 27.6 | 1.06 | (0.91,1.22) | 0.4559 | 1.14 | (0.89,1.46) | |
| Very high | 299 | 82 | 27.4 | 308 | 82 | 26.6 | 1.05 | (0.84,1.32) | 0.6535 | 1.03 | (0.67,1.57) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7629 |
| No | 152 | 38 | 25.0 | 159 | 46 | 28.9 | 1.10 | (0.80,1.52) | 0.5641 | 1.26 | (0.70,2.27) | |
| Yes | 1044 | 263 | 25.2 | 1056 | 288 | 27.3 | 1.04 | (0.91,1.19) | 0.5369 | 1.08 | (0.86,1.36) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6297 |
| No | 57 | 16 | 28.1 | 66 | 19 | 28.8 | 0.93 | (0.55,1.56) | 0.7725 | 0.84 | (0.34,2.07) | |
| Yes | 1139 | 285 | 25.0 | 1149 | 315 | 27.4 | 1.06 | (0.93,1.20) | 0.3903 | 1.12 | (0.90,1.40) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3260 |
| No | 43 | 8 | 18.6 | 54 | 16 | 29.6 | 1.43 | (0.76,2.70) | 0.2652 | 1.83 | (0.61,5.50) | |
| Yes | 1153 | 293 | 25.4 | 1161 | 318 | 27.4 | 1.04 | (0.92,1.17) | 0.5724 | 1.08 | (0.87,1.34) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**R.3.1.2.1.2**

R.3.1.2.1.2 KCCQ-OSS responder analysis (5 points)

Table R.3.1.2.1.2: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -5 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1196 | 323 | 27.0 | 1220 | 289 | 23.7 | 0.88 | (0.77,1.01) | 0.0645 | 0.84 | ( 0.69,1.01) | |
| Sex | | | | | | | | | | | | 0.1869 |
| Male | 906 | 258 | 28.5 | 933 | 220 | 23.6 | 0.84 | (0.72,0.98) | 0.0242 | 0.78 | ( 0.63,0.97) | |
| Female | 290 | 65 | 22.4 | 287 | 69 | 24.0 | 1.05 | (0.78,1.40) | 0.7592 | 1.07 | ( 0.72,1.59) | |
| Age [years] | | | | | | | | | | | | 0.7273 |
| <65 | 412 | 95 | 23.1 | 375 | 81 | 21.6 | 0.92 | (0.71,1.19) | 0.5082 | 0.89 | ( 0.63,1.26) | |
| >=65 | 784 | 228 | 29.1 | 845 | 208 | 24.6 | 0.87 | (0.74,1.02) | 0.0781 | 0.82 | ( 0.65,1.02) | |
| Region^^ | | | | | | | | | | | | NC. |
| North America | 144 | 29 | 20.1 | 155 | 35 | 22.6 | NC. | | | 1.16 | ( 0.66,2.04) | |
| Latin America | 392 | 90 | 23.0 | 409 | 85 | 20.8 | NC. | | | 0.88 | ( 0.63,1.23) | |
| Europe | 445 | 143 | 32.1 | 451 | 131 | 29.0 | NC. | | | 0.86 | ( 0.64,1.14) | |
| Asia | 170 | 54 | 31.8 | 162 | 38 | 23.5 | NC. | | | 0.68 | ( 0.42,1.11) | |
| Other | 45 | 7 | 15.6 | 43 | 0 | 0 | NC. | | | 0.06 | (<0.01,1.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.4057 |
| Diabetic | 652 | 180 | 27.6 | 665 | 153 | 23.0 | 0.84 | (0.70,1.00) | 0.0544 | 0.78 | ( 0.60,1.01) | |
| Non-Diabetic | 544 | 143 | 26.3 | 555 | 136 | 24.5 | 0.94 | (0.77,1.15) | 0.5325 | 0.91 | ( 0.69,1.21) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7950 |
| <30 | 840 | 219 | 26.1 | 797 | 181 | 22.7 | 0.86 | (0.73,1.02) | 0.0854 | 0.82 | ( 0.65,1.03) | |
| >=30 | 356 | 104 | 29.2 | 423 | 108 | 25.5 | 0.90 | (0.71,1.12) | 0.3404 | 0.85 | ( 0.62,1.18) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7655 |
| <130 | 798 | 214 | 26.8 | 790 | 191 | 24.2 | 0.89 | (0.76,1.05) | 0.1851 | 0.86 | ( 0.68,1.08) | |
| >=130 | 398 | 109 | 27.4 | 430 | 98 | 22.8 | 0.86 | (0.68,1.08) | 0.1918 | 0.81 | ( 0.58,1.11) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
^^ Firth´s penalised maximum likelihood estimation used for odds ratios.
N: Number of patients analysed, n: Number of patients with event.
NC. = Not calculated.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.2: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -5 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.9490 |
| <75 | 673 | 196 | 29.1 | 645 | 161 | 25.0 | 0.87 | (0.73,1.04) | 0.1154 | 0.82 | ( 0.64,1.05) | |
| 75 to <85 | 323 | 82 | 25.4 | 362 | 84 | 23.2 | 0.90 | (0.69,1.16) | 0.4052 | 0.86 | ( 0.60,1.23) | |
| >=85 | 200 | 45 | 22.5 | 213 | 44 | 20.7 | 0.92 | (0.64,1.33) | 0.6702 | 0.90 | ( 0.56,1.45) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6530 |
| <30 | 80 | 26 | 32.5 | 108 | 25 | 23.1 | 0.72 | (0.45,1.14) | 0.1566 | 0.62 | ( 0.32,1.21) | |
| 30 to <45 | 336 | 102 | 30.4 | 334 | 91 | 27.2 | 0.88 | (0.70,1.11) | 0.2753 | 0.83 | ( 0.59,1.16) | |
| >=45 | 780 | 195 | 25.0 | 778 | 173 | 22.2 | 0.90 | (0.76,1.08) | 0.2680 | 0.87 | ( 0.69,1.11) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0987 |
| Normal (<30) | 430 | 114 | 26.5 | 442 | 122 | 27.6 | 1.06 | (0.86,1.32) | 0.5835 | 1.09 | ( 0.80,1.48) | |
| Microalbuminuria (30 to <=300) | 580 | 163 | 28.1 | 572 | 127 | 22.2 | 0.79 | (0.64,0.96) | 0.0168 | 0.71 | ( 0.54,0.94) | |
| Macroalbuminuria (>300) | 181 | 46 | 25.4 | 200 | 40 | 20.0 | 0.78 | (0.54,1.12) | 0.1767 | 0.71 | ( 0.43,1.16) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.8307 |
| Low, moderate or high | 892 | 238 | 26.7 | 905 | 213 | 23.5 | 0.89 | (0.76,1.04) | 0.1453 | 0.85 | ( 0.68,1.06) | |
| Very high | 299 | 85 | 28.4 | 310 | 76 | 24.5 | 0.86 | (0.67,1.11) | 0.2498 | 0.81 | ( 0.56,1.16) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.0525 |
| No | 152 | 47 | 30.9 | 159 | 31 | 19.5 | 0.62 | (0.42,0.91) | 0.0142 | 0.51 | ( 0.30,0.87) | |
| Yes | 1044 | 276 | 26.4 | 1061 | 258 | 24.3 | 0.93 | (0.80,1.07) | 0.3014 | 0.90 | ( 0.74,1.10) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.8776 |
| No | 57 | 14 | 24.6 | 66 | 13 | 19.7 | 0.84 | (0.44,1.60) | 0.5936 | 0.79 | ( 0.33,1.90) | |
| Yes | 1139 | 309 | 27.1 | 1154 | 276 | 23.9 | 0.88 | (0.77,1.01) | 0.0768 | 0.84 | ( 0.69,1.02) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
^^ Firth´s penalised maximum likelihood estimation used for odds ratios.
N: Number of patients analysed, n: Number of patients with event.
NC. = Not calculated.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.2: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -5 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | | 0.8926 |
| No | 43 | 7 | 16.3 | 54 | 9 | 16.7 | 0.94 | (0.39,2.26) | 0.8887 | 0.92 | ( 0.31,2.77) | |
| Yes | 1153 | 316 | 27.4 | 1166 | 280 | 24.0 | 0.88 | (0.77,1.01) | 0.0750 | 0.84 | ( 0.69,1.02) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
^^ Firth´s penalised maximum likelihood estimation used for odds ratios.
N: Number of patients analysed, n: Number of patients with event.
NC. = Not calculated.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.2: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatmentperiod >= 5 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1196 | 551 | 46.1 | 1220 | 595 | 48.8 | 1.04 | (0.96,1.13) | 0.3053 | 1.11 | (0.93,1.32) | |
| Sex | | | | | | | | | | | | 0.9671 |
| Male | 906 | 398 | 43.9 | 933 | 440 | 47.2 | 1.04 | (0.95,1.15) | 0.3788 | 1.10 | (0.90,1.34) | |
| Female | 290 | 153 | 52.8 | 287 | 155 | 54.0 | 1.04 | (0.90,1.20) | 0.6005 | 1.14 | (0.80,1.64) | |
| Age [years] | | | | | | | | | | | | 0.5281 |
| <65 | 412 | 215 | 52.2 | 375 | 199 | 53.1 | 1.01 | (0.88,1.14) | 0.9272 | 1.04 | (0.76,1.42) | |
| >=65 | 784 | 336 | 42.9 | 845 | 396 | 46.9 | 1.06 | (0.96,1.17) | 0.2490 | 1.14 | (0.92,1.41) | |
| Region | | | | | | | | | | | | 0.8643 |
| North America | 144 | 60 | 41.7 | 155 | 75 | 48.4 | 1.13 | (0.89,1.43) | 0.3271 | 1.30 | (0.79,2.14) | |
| Latin America | 392 | 227 | 57.9 | 409 | 237 | 57.9 | 0.99 | (0.89,1.11) | 0.9071 | 1.01 | (0.74,1.37) | |
| Europe | 445 | 174 | 39.1 | 451 | 189 | 41.9 | 1.07 | (0.92,1.25) | 0.3691 | 1.16 | (0.87,1.54) | |
| Asia | 170 | 61 | 35.9 | 162 | 67 | 41.4 | 1.07 | (0.83,1.38) | 0.6098 | 1.12 | (0.70,1.79) | |
| Other | 45 | 29 | 64.4 | 43 | 27 | 62.8 | 1.01 | (0.75,1.36) | 0.9357 | 0.96 | (0.39,2.37) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.6222 |
| Diabetic | 652 | 315 | 48.3 | 665 | 334 | 50.2 | 1.02 | (0.92,1.14) | 0.6459 | 1.08 | (0.85,1.37) | |
| Non-Diabetic | 544 | 236 | 43.4 | 555 | 261 | 47.0 | 1.07 | (0.94,1.20) | 0.2973 | 1.15 | (0.89,1.49) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.6060 |
| <30 | 840 | 390 | 46.4 | 797 | 381 | 47.8 | 1.03 | (0.94,1.13) | 0.5184 | 1.08 | (0.88,1.34) | |
| >=30 | 356 | 161 | 45.2 | 423 | 214 | 50.6 | 1.08 | (0.94,1.24) | 0.2943 | 1.20 | (0.88,1.63) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7985 |
| <130 | 798 | 367 | 46.0 | 790 | 383 | 48.5 | 1.05 | (0.95,1.16) | 0.3243 | 1.12 | (0.91,1.39) | |
| >=130 | 398 | 184 | 46.2 | 430 | 212 | 49.3 | 1.03 | (0.90,1.18) | 0.7029 | 1.08 | (0.80,1.46) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.1908 |
| <75 | 673 | 280 | 41.6 | 645 | 306 | 47.4 | 1.11 | (1.00,1.24) | 0.0608 | 1.26 | (0.99,1.59) | |
| 75 to <85 | 323 | 167 | 51.7 | 362 | 173 | 47.8 | 0.95 | (0.82,1.09) | 0.4446 | 0.89 | (0.64,1.23) | |
| >=85 | 200 | 104 | 52.0 | 213 | 116 | 54.5 | 1.00 | (0.84,1.20) | 0.9923 | 1.04 | (0.68,1.59) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.2: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatmentperiod >= 5 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.9091 |
| <30 | 80 | 36 | 45.0 | 108 | 49 | 45.4 | 0.99 | (0.74,1.32) | 0.9360 | 0.96 | (0.51,1.81) | |
| 30 to <45 | 336 | 148 | 44.0 | 334 | 151 | 45.2 | 1.03 | (0.88,1.21) | 0.6806 | 1.10 | (0.79,1.53) | |
| >=45 | 780 | 367 | 47.1 | 778 | 395 | 50.8 | 1.05 | (0.96,1.16) | 0.2818 | 1.14 | (0.91,1.41) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7851 |
| Normal (<30) | 430 | 184 | 42.8 | 442 | 195 | 44.1 | 1.00 | (0.87,1.15) | 0.9945 | 1.00 | (0.75,1.34) | |
| Microalbuminuria (30 to <=300) | 580 | 269 | 46.4 | 572 | 285 | 49.8 | 1.06 | (0.95,1.19) | 0.2822 | 1.18 | (0.92,1.52) | |
| Macroalbuminuria (>300) | 181 | 94 | 51.9 | 200 | 110 | 55.0 | 1.05 | (0.89,1.25) | 0.5437 | 1.14 | (0.73,1.78) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7709 |
| Low, moderate or high | 892 | 406 | 45.5 | 905 | 442 | 48.8 | 1.05 | (0.95,1.15) | 0.3249 | 1.13 | (0.92,1.38) | |
| Very high | 299 | 141 | 47.2 | 310 | 148 | 47.7 | 1.02 | (0.88,1.19) | 0.7939 | 1.03 | (0.72,1.46) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.3646 |
| No | 152 | 73 | 48.0 | 159 | 88 | 55.3 | 1.14 | (0.92,1.41) | 0.2220 | 1.36 | (0.83,2.21) | |
| Yes | 1044 | 478 | 45.8 | 1061 | 507 | 47.8 | 1.03 | (0.94,1.12) | 0.5419 | 1.08 | (0.89,1.30) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.8280 |
| No | 57 | 29 | 50.9 | 66 | 39 | 59.1 | 1.07 | (0.80,1.44) | 0.6374 | 1.27 | (0.58,2.75) | |
| Yes | 1139 | 522 | 45.8 | 1154 | 556 | 48.2 | 1.04 | (0.96,1.13) | 0.3702 | 1.10 | (0.92,1.31) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.5449 |
| No | 43 | 20 | 46.5 | 54 | 28 | 51.9 | 1.17 | (0.79,1.75) | 0.4295 | 1.35 | (0.57,3.24) | |
| Yes | 1153 | 531 | 46.1 | 1166 | 567 | 48.6 | 1.04 | (0.96,1.12) | 0.3938 | 1.10 | (0.92,1.31) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**R.3.1.2.1.3**

R.3.1.2.1.3 KCCQ-OSS responder analysis (15 points)

Table R.3.1.2.1.3: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1196 | 161 | 13.5 | 1220 | 137 | 11.2 | 0.84 | (0.68,1.03) | 0.0956 | 0.81 | ( 0.63,1.04) | |
| Sex | | | | | | | | | | | | 0.1106 |
| Male | 906 | 133 | 14.7 | 933 | 104 | 11.1 | 0.77 | (0.61,0.97) | 0.0274 | 0.73 | ( 0.55,0.96) | |
| Female | 290 | 28 | 9.7 | 287 | 33 | 11.5 | 1.17 | (0.74,1.86) | 0.5046 | 1.20 | ( 0.70,2.07) | |
| Age [years] | | | | | | | | | | | | 0.9370 |
| <65 | 412 | 43 | 10.4 | 375 | 34 | 9.1 | 0.85 | (0.56,1.29) | 0.4442 | 0.83 | ( 0.51,1.35) | |
| >=65 | 784 | 118 | 15.1 | 845 | 103 | 12.2 | 0.83 | (0.65,1.06) | 0.1384 | 0.80 | ( 0.60,1.07) | |
| Region^^ | | | | | | | | | | | | NC. |
| North America | 144 | 13 | 9.0 | 155 | 18 | 11.6 | NC. | | | 1.31 | ( 0.62,2.79) | |
| Latin America | 392 | 48 | 12.2 | 409 | 40 | 9.8 | NC. | | | 0.78 | ( 0.49,1.21) | |
| Europe | 445 | 71 | 16.0 | 451 | 61 | 13.5 | NC. | | | 0.81 | ( 0.56,1.18) | |
| Asia | 170 | 25 | 14.7 | 162 | 18 | 11.1 | NC. | | | 0.75 | ( 0.39,1.44) | |
| Other | 45 | 4 | 8.9 | 43 | 0 | 0 | NC. | | | 0.10 | (<0.01,2.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.7964 |
| Diabetic | 652 | 88 | 13.5 | 665 | 73 | 11.0 | 0.81 | (0.61,1.08) | 0.1585 | 0.78 | ( 0.56,1.10) | |
| Non-Diabetic | 544 | 73 | 13.4 | 555 | 64 | 11.5 | 0.86 | (0.63,1.18) | 0.3465 | 0.84 | ( 0.58,1.21) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.6404 |
| <30 | 840 | 112 | 13.3 | 797 | 93 | 11.7 | 0.86 | (0.67,1.11) | 0.2588 | 0.84 | ( 0.62,1.13) | |
| >=30 | 356 | 49 | 13.8 | 423 | 44 | 10.4 | 0.78 | (0.53,1.13) | 0.1813 | 0.74 | ( 0.48,1.15) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5519 |
| <130 | 798 | 112 | 14.0 | 790 | 90 | 11.4 | 0.80 | (0.62,1.03) | 0.0881 | 0.77 | ( 0.57,1.04) | |
| >=130 | 398 | 49 | 12.3 | 430 | 47 | 10.9 | 0.92 | (0.63,1.33) | 0.6541 | 0.90 | ( 0.59,1.39) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
^^ Firth´s penalised maximum likelihood estimation used for odds ratios.
N: Number of patients analysed, n: Number of patients with event.
NC. = Not calculated.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.3: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4181 |
| <75 | 673 | 109 | 16.2 | 645 | 81 | 12.6 | 0.79 | (0.61,1.03) | 0.0777 | 0.75 | ( 0.55,1.03) | |
| 75 to <85 | 323 | 36 | 11.1 | 362 | 35 | 9.7 | 0.84 | (0.54,1.28) | 0.4118 | 0.81 | ( 0.49,1.34) | |
| >=85 | 200 | 16 | 8.0 | 213 | 21 | 9.9 | 1.25 | (0.67,2.32) | 0.4898 | 1.28 | ( 0.64,2.56) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8447 |
| <30 | 80 | 17 | 21.3 | 108 | 16 | 14.8 | 0.70 | (0.38,1.29) | 0.2540 | 0.64 | ( 0.30,1.39) | |
| 30 to <45 | 336 | 52 | 15.5 | 334 | 45 | 13.5 | 0.86 | (0.60,1.23) | 0.4145 | 0.83 | ( 0.54,1.29) | |
| >=45 | 780 | 92 | 11.8 | 778 | 76 | 9.8 | 0.84 | (0.63,1.12) | 0.2283 | 0.82 | ( 0.59,1.13) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8287 |
| Normal (<30) | 430 | 58 | 13.5 | 442 | 49 | 11.1 | 0.84 | (0.59,1.20) | 0.3402 | 0.82 | ( 0.54,1.24) | |
| Microalbuminuria (30 to <=300) | 580 | 81 | 14.0 | 572 | 70 | 12.2 | 0.87 | (0.65,1.17) | 0.3523 | 0.85 | ( 0.59,1.20) | |
| Macroalbuminuria (>300) | 181 | 22 | 12.2 | 200 | 18 | 9.0 | 0.71 | (0.40,1.27) | 0.2505 | 0.67 | ( 0.34,1.31) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.9933 |
| Low, moderate or high | 892 | 110 | 12.3 | 905 | 93 | 10.3 | 0.84 | (0.65,1.08) | 0.1781 | 0.81 | ( 0.61,1.10) | |
| Very high | 299 | 51 | 17.1 | 310 | 44 | 14.2 | 0.84 | (0.58,1.20) | 0.3329 | 0.80 | ( 0.51,1.25) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.0321 |
| No | 152 | 26 | 17.1 | 159 | 13 | 8.2 | 0.45 | (0.24,0.83) | 0.0103 | 0.39 | ( 0.19,0.80) | |
| Yes | 1044 | 135 | 12.9 | 1061 | 124 | 11.7 | 0.92 | (0.73,1.15) | 0.4389 | 0.90 | ( 0.69,1.17) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3269 |
| No | 57 | 9 | 15.8 | 66 | 5 | 7.6 | 0.51 | (0.19,1.39) | 0.1910 | 0.46 | ( 0.14,1.49) | |
| Yes | 1139 | 152 | 13.3 | 1154 | 132 | 11.4 | 0.86 | (0.69,1.06) | 0.1578 | 0.83 | ( 0.65,1.07) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
^^ Firth´s penalised maximum likelihood estimation used for odds ratios.
N: Number of patients analysed, n: Number of patients with event.
NC. = Not calculated.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.3: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | | 0.3223 |
| No | 43 | 5 | 11.6 | 54 | 3 | 5.6 | 0.43 | (0.11,1.67) | 0.2206 | 0.39 | ( 0.09,1.75) | |
| Yes | 1153 | 156 | 13.5 | 1166 | 134 | 11.5 | 0.86 | (0.69,1.06) | 0.1544 | 0.83 | ( 0.65,1.07) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
^^ Firth´s penalised maximum likelihood estimation used for odds ratios.
N: Number of patients analysed, n: Number of patients with event.
NC. = Not calculated.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.3: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1196 | 293 | 24.5 | 1220 | 333 | 27.3 | 1.07 | (0.94,1.21) | 0.3165 | 1.14 | (0.93,1.41) | |
| Sex | | | | | | | | | | | | 0.2291 |
| Male | 906 | 210 | 23.2 | 933 | 234 | 25.1 | 1.01 | (0.87,1.18) | 0.8458 | 1.04 | (0.82,1.33) | |
| Female | 290 | 83 | 28.6 | 287 | 99 | 34.5 | 1.20 | (0.96,1.51) | 0.1153 | 1.48 | (0.99,2.23) | |
| Age [years] | | | | | | | | | | | | 0.6095 |
| <65 | 412 | 122 | 29.6 | 375 | 117 | 31.2 | 1.02 | (0.83,1.25) | 0.8699 | 1.08 | (0.76,1.54) | |
| >=65 | 784 | 171 | 21.8 | 845 | 216 | 25.6 | 1.09 | (0.93,1.28) | 0.2926 | 1.17 | (0.90,1.52) | |
| Region | | | | | | | | | | | | 0.7507 |
| North America | 144 | 27 | 18.8 | 155 | 40 | 25.8 | 1.27 | (0.85,1.89) | 0.2367 | 1.53 | (0.82,2.86) | |
| Latin America | 392 | 147 | 37.5 | 409 | 160 | 39.1 | 1.01 | (0.86,1.20) | 0.8925 | 1.08 | (0.78,1.49) | |
| Europe | 445 | 79 | 17.8 | 451 | 89 | 19.7 | 1.10 | (0.85,1.43) | 0.4583 | 1.17 | (0.81,1.69) | |
| Asia | 170 | 25 | 14.7 | 162 | 33 | 20.4 | 1.17 | (0.76,1.79) | 0.4764 | 1.21 | (0.65,2.24) | |
| Other | 45 | 15 | 33.3 | 43 | 11 | 25.6 | 0.84 | (0.45,1.57) | 0.5776 | 0.70 | (0.26,1.92) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9742 |
| Diabetic | 652 | 163 | 25.0 | 665 | 186 | 28.0 | 1.07 | (0.90,1.27) | 0.4382 | 1.15 | (0.86,1.52) | |
| Non-Diabetic | 544 | 130 | 23.9 | 555 | 147 | 26.5 | 1.06 | (0.89,1.28) | 0.4997 | 1.15 | (0.84,1.56) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.8798 |
| <30 | 840 | 202 | 24.0 | 797 | 206 | 25.8 | 1.06 | (0.91,1.23) | 0.4524 | 1.14 | (0.88,1.47) | |
| >=30 | 356 | 91 | 25.6 | 423 | 127 | 30.0 | 1.08 | (0.87,1.35) | 0.4790 | 1.17 | (0.81,1.67) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8662 |
| <130 | 798 | 200 | 25.1 | 790 | 213 | 27.0 | 1.06 | (0.91,1.23) | 0.4545 | 1.12 | (0.87,1.45) | |
| >=130 | 398 | 93 | 23.4 | 430 | 120 | 27.9 | 1.08 | (0.87,1.35) | 0.4750 | 1.20 | (0.83,1.72) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.1565 |
| <75 | 673 | 144 | 21.4 | 645 | 174 | 27.0 | 1.18 | (0.99,1.41) | 0.0604 | 1.35 | (1.01,1.80) | |
| 75 to <85 | 323 | 95 | 29.4 | 362 | 91 | 25.1 | 0.90 | (0.72,1.12) | 0.3363 | 0.82 | (0.55,1.21) | |
| >=85 | 200 | 54 | 27.0 | 213 | 68 | 31.9 | 1.05 | (0.79,1.41) | 0.7243 | 1.19 | (0.73,1.95) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.3.1.2.1.3: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.7327 |
| <30 | 80 | 14 | 17.5 | 108 | 22 | 20.4 | 1.13 | (0.69,1.87) | 0.6286 | 1.24 | (0.53,2.87) | |
| 30 to <45 | 336 | 67 | 19.9 | 334 | 80 | 24.0 | 1.17 | (0.90,1.53) | 0.2345 | 1.36 | (0.90,2.05) | |
| >=45 | 780 | 212 | 27.2 | 778 | 231 | 29.7 | 1.04 | (0.90,1.21) | 0.5689 | 1.07 | (0.83,1.38) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4997 |
| Normal (<30) | 430 | 95 | 22.1 | 442 | 102 | 23.1 | 0.99 | (0.79,1.23) | 0.8984 | 0.98 | (0.68,1.40) | |
| Microalbuminuria (30 to <=300) | 580 | 142 | 24.5 | 572 | 168 | 29.4 | 1.14 | (0.95,1.37) | 0.1517 | 1.34 | (0.99,1.81) | |
| Macroalbuminuria (>300) | 181 | 54 | 29.8 | 200 | 59 | 29.5 | 0.97 | (0.74,1.29) | 0.8582 | 0.94 | (0.57,1.56) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7004 |
| Low, moderate or high | 892 | 227 | 25.4 | 905 | 255 | 28.2 | 1.05 | (0.91,1.21) | 0.5106 | 1.11 | (0.87,1.40) | |
| Very high | 299 | 64 | 21.4 | 310 | 74 | 23.9 | 1.11 | (0.86,1.44) | 0.4236 | 1.20 | (0.77,1.85) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6886 |
| No | 152 | 39 | 25.7 | 159 | 47 | 29.6 | 1.14 | (0.82,1.58) | 0.4509 | 1.22 | (0.69,2.16) | |
| Yes | 1044 | 254 | 24.3 | 1061 | 286 | 27.0 | 1.06 | (0.92,1.21) | 0.4312 | 1.13 | (0.91,1.42) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9408 |
| No | 57 | 13 | 22.8 | 66 | 20 | 30.3 | 1.09 | (0.62,1.92) | 0.7748 | 1.24 | (0.50,3.05) | |
| Yes | 1139 | 280 | 24.6 | 1154 | 313 | 27.1 | 1.06 | (0.93,1.21) | 0.3521 | 1.14 | (0.92,1.41) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.5398 |
| No | 43 | 8 | 18.6 | 54 | 13 | 24.1 | 1.33 | (0.64,2.75) | 0.4395 | 1.47 | (0.48,4.48) | |
| Yes | 1153 | 285 | 24.7 | 1166 | 320 | 27.4 | 1.06 | (0.93,1.20) | 0.3885 | 1.13 | (0.92,1.40) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, baseline LVEF, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**R.3.2**

**R.3.2.1**

R.3.2.1 Adverse events overall

Table R.3.2.1: 1 Proportion of patients with any adverse event occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 1061 | 83.3 | 1278 | 1030 | 80.6 | 0.0778 | 0.97 | (0.93,>1.00) | 0.83 | (0.68,1.02) | -0.03 | (-0.06, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.9900 |
| Male | 958 | 799 | 83.4 | 975 | 787 | 80.7 | 0.1241 | 0.97 | (0.93, 1.01) | 0.83 | (0.66,1.05) | -0.03 | (-0.06, 0.01) | |
| Female | 316 | 262 | 82.9 | 303 | 243 | 80.2 | 0.3840 | 0.97 | (0.90, 1.04) | 0.83 | (0.56,1.25) | -0.03 | (-0.09, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.0758 |
| <65 | 435 | 344 | 79.1 | 392 | 315 | 80.4 | 0.6486 | 1.02 | (0.95, 1.09) | 1.08 | (0.77,1.52) | 0.01 | (-0.04, 0.07) | |
| >=65 | 839 | 717 | 85.5 | 886 | 715 | 80.7 | 0.0085 | 0.94 | (0.90, 0.99) | 0.71 | (0.55,0.92) | -0.05 | (-0.08,-0.01) | |
| Region | | | | | | | | | | | | | | 0.8539 |
| North America | 161 | 146 | 90.7 | 159 | 137 | 86.2 | 0.2062 | 0.95 | (0.88, 1.03) | 0.64 | (0.32,1.28) | -0.05 | (-0.12, 0.02) | |
| Latin America | 420 | 338 | 80.5 | 440 | 335 | 76.1 | 0.1230 | 0.95 | (0.88, 1.02) | 0.77 | (0.56,1.07) | -0.04 | (-0.10, 0.01) | |
| Europe | 469 | 378 | 80.6 | 467 | 372 | 79.7 | 0.7187 | 0.99 | (0.93, 1.05) | 0.94 | (0.68,1.30) | -0.01 | (-0.06, 0.04) | |
| Asia | 174 | 160 | 92.0 | 165 | 149 | 90.3 | 0.5927 | 0.98 | (0.92, 1.05) | 0.81 | (0.38,1.73) | -0.02 | (-0.08, 0.04) | |
| Other | 50 | 39 | 78.0 | 47 | 37 | 78.7 | 0.9311 | 1.01 | (0.82, 1.24) | 1.04 | (0.40,2.75) | 0.01 | (-0.16, 0.17) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8769 |
| Diabetic | 694 | 580 | 83.6 | 698 | 566 | 81.1 | 0.2243 | 0.97 | (0.92, 1.02) | 0.84 | (0.64,1.11) | -0.02 | (-0.06, 0.02) | |
| Non-Diabetic | 580 | 481 | 82.9 | 580 | 464 | 80.0 | 0.1990 | 0.96 | (0.91, 1.02) | 0.82 | (0.61,1.11) | -0.03 | (-0.07, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8737 |
| <30 | 889 | 743 | 83.6 | 836 | 678 | 81.1 | 0.1773 | 0.97 | (0.93, 1.01) | 0.84 | (0.66,1.08) | -0.02 | (-0.06, 0.01) | |
| >=30 | 385 | 318 | 82.6 | 442 | 352 | 79.6 | 0.2791 | 0.96 | (0.90, 1.03) | 0.82 | (0.58,1.17) | -0.03 | (-0.08, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6307 |
| <130 | 857 | 718 | 83.8 | 834 | 672 | 80.6 | 0.0850 | 0.96 | (0.92, 1.01) | 0.80 | (0.63,1.03) | -0.03 | (-0.07, 0.00) | |
| >=130 | 417 | 343 | 82.3 | 444 | 358 | 80.6 | 0.5405 | 0.98 | (0.92, 1.04) | 0.90 | (0.64,1.27) | -0.02 | (-0.07, 0.04) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4965 |
| <75 | 718 | 607 | 84.5 | 678 | 566 | 83.5 | 0.5892 | 0.99 | (0.94, 1.03) | 0.92 | (0.69,1.23) | -0.01 | (-0.05, 0.03) | |
| 75 to <85 | 348 | 281 | 80.7 | 382 | 295 | 77.2 | 0.2440 | 0.96 | (0.89, 1.03) | 0.81 | (0.57,1.16) | -0.04 | (-0.09, 0.02) | |
| >=85 | 208 | 173 | 83.2 | 218 | 169 | 77.5 | 0.1429 | 0.93 | (0.85, 1.02) | 0.70 | (0.43,1.13) | -0.06 | (-0.13, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 1 Proportion of patients with any adverse event occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0018 |
| <30 | 89 | 80 | 89.9 | 115 | 108 | 93.9 | 0.2889 | 1.04 | (0.96, 1.14) | 1.74 | (0.62,4.86) | 0.04 | (-0.04, 0.12) | |
| 30 to <45 | 348 | 312 | 89.7 | 345 | 272 | 78.8 | <0.0001 | 0.88 | (0.82, 0.94) | 0.43 | (0.28,0.66) | -0.11 | (-0.16,-0.05) | |
| >=45 | 837 | 669 | 79.9 | 818 | 650 | 79.5 | 0.8136 | 0.99 | (0.95, 1.04) | 0.97 | (0.76,1.23) | 0.00 | (-0.04, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7910 |
| Normal (<30) | 452 | 362 | 80.1 | 456 | 359 | 78.7 | 0.6123 | 0.98 | (0.92, 1.05) | 0.92 | (0.67,1.27) | -0.01 | (-0.07, 0.04) | |
| Microalbuminuria (30 to <=300) | 627 | 530 | 84.5 | 608 | 492 | 80.9 | 0.0933 | 0.96 | (0.91, 1.01) | 0.78 | (0.58,1.04) | -0.04 | (-0.08, 0.01) | |
| Macroalbuminuria (>300) | 189 | 165 | 87.3 | 207 | 177 | 85.5 | 0.6033 | 0.98 | (0.91, 1.06) | 0.86 | (0.48,1.53) | -0.02 | (-0.09, 0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.6756 |
| Low, moderate or high | 953 | 771 | 80.9 | 947 | 746 | 78.8 | 0.2478 | 0.97 | (0.93, 1.02) | 0.88 | (0.70,1.10) | -0.02 | (-0.06, 0.01) | |
| Very high | 315 | 286 | 90.8 | 325 | 283 | 87.1 | 0.1344 | 0.96 | (0.91, 1.01) | 0.68 | (0.41,1.13) | -0.04 | (-0.09, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.8294 |
| No | 161 | 139 | 86.3 | 168 | 139 | 82.7 | 0.3675 | 0.96 | (0.87, 1.05) | 0.76 | (0.42,1.39) | -0.04 | (-0.11, 0.04) | |
| Yes | 1113 | 922 | 82.8 | 1110 | 891 | 80.3 | 0.1184 | 0.97 | (0.93, 1.01) | 0.84 | (0.68,1.04) | -0.03 | (-0.06, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7434 |
| No | 62 | 54 | 87.1 | 72 | 62 | 86.1 | 0.8675 | 0.99 | (0.87, 1.13) | 0.92 | (0.34,2.49) | -0.01 | (-0.13, 0.11) | |
| Yes | 1212 | 1007 | 83.1 | 1206 | 968 | 80.3 | 0.0730 | 0.97 | (0.93,>1.00) | 0.83 | (0.67,1.02) | -0.03 | (-0.06, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1926 |
| No | 46 | 39 | 84.8 | 57 | 41 | 71.9 | 0.1194 | 0.85 | (0.69, 1.04) | 0.46 | (0.17,1.24) | -0.13 | (-0.28, 0.03) | |
| Yes | 1228 | 1022 | 83.2 | 1221 | 989 | 81.0 | 0.1507 | 0.97 | (0.94, 1.01) | 0.86 | (0.70,1.06) | -0.02 | (-0.05, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 986 | 77.4 | 1278 | 961 | 75.2 | 0.1917 | 0.97 | (0.93, 1.01) | 0.89 | (0.74,1.06) | -0.02 | (-0.05, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.8501 |
| Male | 958 | 742 | 77.5 | 975 | 732 | 75.1 | 0.2196 | 0.97 | (0.92, 1.02) | 0.88 | (0.71,1.08) | -0.02 | (-0.06, 0.01) | |
| Female | 316 | 244 | 77.2 | 303 | 229 | 75.6 | 0.6314 | 0.98 | (0.90, 1.07) | 0.91 | (0.63,1.32) | -0.02 | (-0.08, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.1159 |
| <65 | 435 | 318 | 73.1 | 392 | 293 | 74.7 | 0.5916 | 1.02 | (0.94, 1.11) | 1.09 | (0.80,1.49) | 0.02 | (-0.04, 0.08) | |
| >=65 | 839 | 668 | 79.6 | 886 | 668 | 75.4 | 0.0359 | 0.95 | (0.90,<1.00) | 0.78 | (0.63,0.98) | -0.04 | (-0.08, 0.00) | |
| Region | | | | | | | | | | | | | | 0.6044 |
| North America | 161 | 136 | 84.5 | 159 | 134 | 84.3 | 0.9616 | 1.00 | (0.91, 1.10) | 0.99 | (0.54,1.80) | 0.00 | (-0.08, 0.08) | |
| Latin America | 420 | 309 | 73.6 | 440 | 298 | 67.7 | 0.0601 | 0.92 | (0.84,>1.00) | 0.75 | (0.56,1.01) | -0.06 | (-0.12, 0.00) | |
| Europe | 469 | 348 | 74.2 | 467 | 347 | 74.3 | 0.9711 | 1.00 | (0.93, 1.08) | 1.01 | (0.75,1.35) | 0.00 | (-0.05, 0.06) | |
| Asia | 174 | 156 | 89.7 | 165 | 146 | 88.5 | 0.7298 | 0.99 | (0.92, 1.06) | 0.89 | (0.45,1.76) | -0.01 | (-0.08, 0.05) | |
| Other | 50 | 37 | 74.0 | 47 | 36 | 76.6 | 0.7672 | 1.04 | (0.82, 1.30) | 1.15 | (0.46,2.90) | 0.03 | (-0.15, 0.20) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2928 |
| Diabetic | 694 | 532 | 76.7 | 698 | 531 | 76.1 | 0.7981 | 0.99 | (0.94, 1.05) | 0.97 | (0.76,1.24) | -0.01 | (-0.05, 0.04) | |
| Non-Diabetic | 580 | 454 | 78.3 | 580 | 430 | 74.1 | 0.0980 | 0.95 | (0.89, 1.01) | 0.80 | (0.61,1.04) | -0.04 | (-0.09, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9358 |
| <30 | 889 | 693 | 78.0 | 836 | 633 | 75.7 | 0.2712 | 0.97 | (0.92, 1.02) | 0.88 | (0.70,1.10) | -0.02 | (-0.06, 0.02) | |
| >=30 | 385 | 293 | 76.1 | 442 | 328 | 74.2 | 0.5295 | 0.98 | (0.90, 1.05) | 0.90 | (0.66,1.24) | -0.02 | (-0.08, 0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3317 |
| <130 | 857 | 668 | 77.9 | 834 | 622 | 74.6 | 0.1037 | 0.96 | (0.91, 1.01) | 0.83 | (0.66,1.04) | -0.03 | (-0.07, 0.01) | |
| >=130 | 417 | 318 | 76.3 | 444 | 339 | 76.4 | 0.9746 | 1.00 | (0.93, 1.08) | 1.01 | (0.73,1.38) | 0.00 | (-0.06, 0.06) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5149 |
| <75 | 718 | 563 | 78.4 | 678 | 529 | 78.0 | 0.8604 | 1.00 | (0.94, 1.05) | 0.98 | (0.76,1.26) | 0.00 | (-0.05, 0.04) | |
| 75 to <85 | 348 | 257 | 73.9 | 382 | 269 | 70.4 | 0.3021 | 0.95 | (0.87, 1.04) | 0.84 | (0.61,1.17) | -0.03 | (-0.10, 0.03) | |
| >=85 | 208 | 166 | 79.8 | 218 | 163 | 74.8 | 0.2153 | 0.94 | (0.85, 1.04) | 0.75 | (0.48,1.18) | -0.05 | (-0.13, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0119 |
| <30 | 89 | 76 | 85.4 | 115 | 103 | 89.6 | 0.3675 | 1.05 | (0.94, 1.17) | 1.47 | (0.63,3.40) | 0.04 | (-0.05, 0.13) | |
| 30 to <45 | 348 | 289 | 83.0 | 345 | 252 | 73.0 | 0.0015 | 0.88 | (0.81, 0.95) | 0.55 | (0.38,0.80) | -0.10 | (-0.16,-0.04) | |
| >=45 | 837 | 621 | 74.2 | 818 | 606 | 74.1 | 0.9591 | 1.00 | (0.94, 1.06) | 0.99 | (0.80,1.24) | 0.00 | (-0.04, 0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9627 |
| Normal (<30) | 452 | 341 | 75.4 | 456 | 337 | 73.9 | 0.5939 | 0.98 | (0.91, 1.06) | 0.92 | (0.68,1.24) | -0.02 | (-0.07, 0.04) | |
| Microalbuminuria (30 to <=300) | 627 | 487 | 77.7 | 608 | 457 | 75.2 | 0.2993 | 0.97 | (0.91, 1.03) | 0.87 | (0.67,1.13) | -0.03 | (-0.07, 0.02) | |
| Macroalbuminuria (>300) | 189 | 156 | 82.5 | 207 | 165 | 79.7 | 0.4729 | 0.97 | (0.88, 1.06) | 0.83 | (0.50,1.38) | -0.03 | (-0.11, 0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2596 |
| Low, moderate or high | 953 | 712 | 74.7 | 947 | 697 | 73.6 | 0.5803 | 0.99 | (0.93, 1.04) | 0.94 | (0.77,1.16) | -0.01 | (-0.05, 0.03) | |
| Very high | 315 | 272 | 86.3 | 325 | 263 | 80.9 | 0.0639 | 0.94 | (0.87,>1.00) | 0.67 | (0.44,1.03) | -0.05 | (-0.11, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.8023 |
| No | 161 | 129 | 80.1 | 168 | 129 | 76.8 | 0.4618 | 0.96 | (0.86, 1.07) | 0.82 | (0.48,1.39) | -0.03 | (-0.12, 0.06) | |
| Yes | 1113 | 857 | 77.0 | 1110 | 832 | 75.0 | 0.2593 | 0.97 | (0.93, 1.02) | 0.89 | (0.74,1.09) | -0.02 | (-0.06, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5715 |
| No | 62 | 49 | 79.0 | 72 | 58 | 80.6 | 0.8265 | 1.02 | (0.86, 1.21) | 1.10 | (0.47,2.56) | 0.02 | (-0.12, 0.15) | |
| Yes | 1212 | 937 | 77.3 | 1206 | 903 | 74.9 | 0.1605 | 0.97 | (0.93, 1.01) | 0.87 | (0.73,1.05) | -0.02 | (-0.06, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5147 |
| No | 46 | 35 | 76.1 | 57 | 39 | 68.4 | 0.3898 | 0.90 | (0.71, 1.14) | 0.68 | (0.28,1.64) | -0.08 | (-0.25, 0.10) | |
| Yes | 1228 | 951 | 77.4 | 1221 | 922 | 75.5 | 0.2599 | 0.98 | (0.93, 1.02) | 0.90 | (0.75,1.08) | -0.02 | (-0.05, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 3 Proportion of patients with serious adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 709 | 55.7 | 1278 | 636 | 49.8 | 0.0029 | 0.89 | (0.83, 0.96) | 0.79 | (0.68,0.92) | -0.06 | (-0.10,-0.02) | |
| Sex | | | | | | | | | | | | | | 0.2917 |
| Male | 958 | 539 | 56.3 | 975 | 501 | 51.4 | 0.0315 | 0.91 | (0.84, 0.99) | 0.82 | (0.69,0.98) | -0.05 | (-0.09, 0.00) | |
| Female | 316 | 170 | 53.8 | 303 | 135 | 44.6 | 0.0215 | 0.83 | (0.70, 0.97) | 0.69 | (0.50,0.95) | -0.09 | (-0.17,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3380 |
| <65 | 435 | 239 | 54.9 | 392 | 182 | 46.4 | 0.0145 | 0.85 | (0.74, 0.97) | 0.71 | (0.54,0.93) | -0.09 | (-0.15,-0.02) | |
| >=65 | 839 | 470 | 56.0 | 886 | 454 | 51.2 | 0.0467 | 0.91 | (0.84,<1.00) | 0.83 | (0.68,1.00) | -0.05 | (-0.09, 0.00) | |
| Region | | | | | | | | | | | | | | 0.6268 |
| North America | 161 | 104 | 64.6 | 159 | 95 | 59.7 | 0.3712 | 0.92 | (0.78, 1.10) | 0.81 | (0.52,1.28) | -0.05 | (-0.15, 0.06) | |
| Latin America | 420 | 221 | 52.6 | 440 | 203 | 46.1 | 0.0573 | 0.88 | (0.77,>1.00) | 0.77 | (0.59,1.01) | -0.06 | (-0.13, 0.00) | |
| Europe | 469 | 251 | 53.5 | 467 | 236 | 50.5 | 0.3611 | 0.94 | (0.83, 1.07) | 0.89 | (0.69,1.15) | -0.03 | (-0.09, 0.03) | |
| Asia | 174 | 112 | 64.4 | 165 | 89 | 53.9 | 0.0508 | 0.84 | (0.70,>1.00) | 0.65 | (0.42,1.00) | -0.10 | (-0.21, 0.00) | |
| Other | 50 | 21 | 42.0 | 47 | 13 | 27.7 | 0.1390 | 0.66 | (0.37, 1.16) | 0.53 | (0.23,1.24) | -0.14 | (-0.33, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3453 |
| Diabetic | 694 | 390 | 56.2 | 698 | 362 | 51.9 | 0.1048 | 0.92 | (0.84, 1.02) | 0.84 | (0.68,1.04) | -0.04 | (-0.10, 0.01) | |
| Non-Diabetic | 580 | 319 | 55.0 | 580 | 274 | 47.2 | 0.0082 | 0.86 | (0.77, 0.96) | 0.73 | (0.58,0.92) | -0.08 | (-0.13,-0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5396 |
| <30 | 889 | 500 | 56.2 | 836 | 414 | 49.5 | 0.0052 | 0.88 | (0.80, 0.96) | 0.76 | (0.63,0.92) | -0.07 | (-0.11,-0.02) | |
| >=30 | 385 | 209 | 54.3 | 442 | 222 | 50.2 | 0.2437 | 0.93 | (0.81, 1.05) | 0.85 | (0.65,1.12) | -0.04 | (-0.11, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3262 |
| <130 | 857 | 488 | 56.9 | 834 | 414 | 49.6 | 0.0026 | 0.87 | (0.80, 0.95) | 0.75 | (0.62,0.90) | -0.07 | (-0.12,-0.03) | |
| >=130 | 417 | 221 | 53.0 | 444 | 222 | 50.0 | 0.3791 | 0.94 | (0.83, 1.07) | 0.89 | (0.68,1.16) | -0.03 | (-0.10, 0.04) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2274 |
| <75 | 718 | 405 | 56.4 | 678 | 363 | 53.5 | 0.2819 | 0.95 | (0.86, 1.04) | 0.89 | (0.72,1.10) | -0.03 | (-0.08, 0.02) | |
| 75 to <85 | 348 | 186 | 53.4 | 382 | 171 | 44.8 | 0.0191 | 0.84 | (0.72, 0.97) | 0.71 | (0.53,0.94) | -0.09 | (-0.16,-0.01) | |
| >=85 | 208 | 118 | 56.7 | 218 | 102 | 46.8 | 0.0401 | 0.82 | (0.69, 0.99) | 0.67 | (0.46,0.98) | -0.10 | (-0.19, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 3 Proportion of patients with serious adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0371 |
| <30 | 89 | 55 | 61.8 | 115 | 81 | 70.4 | 0.1944 | 1.14 | (0.93, 1.39) | 1.47 | (0.82,2.65) | 0.09 | (-0.04, 0.22) | |
| 30 to <45 | 348 | 198 | 56.9 | 345 | 176 | 51.0 | 0.1203 | 0.90 | (0.78, 1.03) | 0.79 | (0.58,1.06) | -0.06 | (-0.13, 0.02) | |
| >=45 | 837 | 456 | 54.5 | 818 | 379 | 46.3 | 0.0009 | 0.85 | (0.77, 0.94) | 0.72 | (0.59,0.88) | -0.08 | (-0.13,-0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6258 |
| Normal (<30) | 452 | 227 | 50.2 | 456 | 199 | 43.6 | 0.0469 | 0.87 | (0.76,<1.00) | 0.77 | (0.59,1.00) | -0.07 | (-0.13, 0.00) | |
| Microalbuminuria (30 to <=300) | 627 | 358 | 57.1 | 608 | 309 | 50.8 | 0.0270 | 0.89 | (0.80, 0.99) | 0.78 | (0.62,0.97) | -0.06 | (-0.12,-0.01) | |
| Macroalbuminuria (>300) | 189 | 120 | 63.5 | 207 | 126 | 60.9 | 0.5910 | 0.96 | (0.82, 1.12) | 0.89 | (0.60,1.34) | -0.03 | (-0.12, 0.07) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0107 |
| Low, moderate or high | 953 | 512 | 53.7 | 947 | 430 | 45.4 | 0.0003 | 0.85 | (0.77, 0.93) | 0.72 | (0.60,0.86) | -0.08 | (-0.13,-0.04) | |
| Very high | 315 | 193 | 61.3 | 325 | 205 | 63.1 | 0.6374 | 1.03 | (0.91, 1.16) | 1.08 | (0.78,1.49) | 0.02 | (-0.06, 0.09) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3434 |
| No | 161 | 98 | 60.9 | 168 | 99 | 58.9 | 0.7195 | 0.97 | (0.81, 1.16) | 0.92 | (0.59,1.43) | -0.02 | (-0.13, 0.09) | |
| Yes | 1113 | 611 | 54.9 | 1110 | 537 | 48.4 | 0.0021 | 0.88 | (0.81, 0.96) | 0.77 | (0.65,0.91) | -0.07 | (-0.11,-0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5209 |
| No | 62 | 36 | 58.1 | 72 | 41 | 56.9 | 0.8960 | 0.98 | (0.73, 1.31) | 0.96 | (0.48,1.90) | -0.01 | (-0.18, 0.16) | |
| Yes | 1212 | 673 | 55.5 | 1206 | 595 | 49.3 | 0.0023 | 0.89 | (0.82, 0.96) | 0.78 | (0.66,0.92) | -0.06 | (-0.10,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.0945 |
| No | 46 | 25 | 54.3 | 57 | 19 | 33.3 | 0.0321 | 0.61 | (0.39, 0.96) | 0.42 | (0.19,0.93) | -0.21 | (-0.40,-0.02) | |
| Yes | 1228 | 684 | 55.7 | 1221 | 617 | 50.5 | 0.0104 | 0.91 | (0.84, 0.98) | 0.81 | (0.69,0.95) | -0.05 | (-0.09,-0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 493 | 38.7 | 1278 | 455 | 35.6 | 0.1057 | 0.92 | (0.83, 1.02) | 0.88 | (0.75,1.03) | -0.03 | (-0.07, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.9568 |
| Male | 958 | 379 | 39.6 | 975 | 354 | 36.3 | 0.1404 | 0.92 | (0.82, 1.03) | 0.87 | (0.72,1.05) | -0.03 | (-0.08, 0.01) | |
| Female | 316 | 114 | 36.1 | 303 | 101 | 33.3 | 0.4737 | 0.92 | (0.74, 1.15) | 0.89 | (0.64,1.23) | -0.03 | (-0.10, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.3287 |
| <65 | 435 | 160 | 36.8 | 392 | 122 | 31.1 | 0.0865 | 0.85 | (0.70, 1.03) | 0.78 | (0.58,1.04) | -0.06 | (-0.12, 0.01) | |
| >=65 | 839 | 333 | 39.7 | 886 | 333 | 37.6 | 0.3693 | 0.95 | (0.84, 1.07) | 0.92 | (0.75,1.11) | -0.02 | (-0.07, 0.02) | |
| Region | | | | | | | | | | | | | | 0.5037 |
| North America | 161 | 79 | 49.1 | 159 | 81 | 50.9 | 0.7373 | 1.04 | (0.83, 1.29) | 1.08 | (0.70,1.67) | 0.02 | (-0.09, 0.13) | |
| Latin America | 420 | 146 | 34.8 | 440 | 127 | 28.9 | 0.0632 | 0.83 | (0.68, 1.01) | 0.76 | (0.57,1.02) | -0.06 | (-0.12, 0.00) | |
| Europe | 469 | 175 | 37.3 | 467 | 171 | 36.6 | 0.8253 | 0.98 | (0.83, 1.16) | 0.97 | (0.74,1.27) | -0.01 | (-0.07, 0.05) | |
| Asia | 174 | 78 | 44.8 | 165 | 66 | 40.0 | 0.3688 | 0.89 | (0.70, 1.14) | 0.82 | (0.53,1.26) | -0.05 | (-0.15, 0.06) | |
| Other | 50 | 15 | 30.0 | 47 | 10 | 21.3 | 0.3263 | 0.71 | (0.35, 1.42) | 0.63 | (0.25,1.59) | -0.09 | (-0.26, 0.09) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0249 |
| Diabetic | 694 | 258 | 37.2 | 698 | 265 | 38.0 | 0.7610 | 1.02 | (0.89, 1.17) | 1.03 | (0.83,1.28) | 0.01 | (-0.04, 0.06) | |
| Non-Diabetic | 580 | 235 | 40.5 | 580 | 190 | 32.8 | 0.0061 | 0.81 | (0.69, 0.94) | 0.72 | (0.56,0.91) | -0.08 | (-0.13,-0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9720 |
| <30 | 889 | 346 | 38.9 | 836 | 300 | 35.9 | 0.1931 | 0.92 | (0.82, 1.04) | 0.88 | (0.72,1.07) | -0.03 | (-0.08, 0.02) | |
| >=30 | 385 | 147 | 38.2 | 442 | 155 | 35.1 | 0.3535 | 0.92 | (0.77, 1.10) | 0.87 | (0.66,1.16) | -0.03 | (-0.10, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2105 |
| <130 | 857 | 335 | 39.1 | 834 | 286 | 34.3 | 0.0408 | 0.88 | (0.77, 0.99) | 0.81 | (0.67,0.99) | -0.05 | (-0.09, 0.00) | |
| >=130 | 417 | 158 | 37.9 | 444 | 169 | 38.1 | 0.9582 | 1.00 | (0.85, 1.19) | 1.01 | (0.76,1.33) | 0.00 | (-0.06, 0.07) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7310 |
| <75 | 718 | 285 | 39.7 | 678 | 257 | 37.9 | 0.4933 | 0.95 | (0.84, 1.09) | 0.93 | (0.75,1.15) | -0.02 | (-0.07, 0.03) | |
| 75 to <85 | 348 | 125 | 35.9 | 382 | 119 | 31.2 | 0.1726 | 0.87 | (0.71, 1.06) | 0.81 | (0.59,1.10) | -0.05 | (-0.12, 0.02) | |
| >=85 | 208 | 83 | 39.9 | 218 | 79 | 36.2 | 0.4360 | 0.91 | (0.71, 1.16) | 0.86 | (0.58,1.27) | -0.04 | (-0.13, 0.06) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1313 |
| <30 | 89 | 38 | 42.7 | 115 | 60 | 52.2 | 0.1791 | 1.22 | (0.91, 1.65) | 1.46 | (0.84,2.56) | 0.09 | (-0.04, 0.23) | |
| 30 to <45 | 348 | 133 | 38.2 | 345 | 119 | 34.5 | 0.3080 | 0.90 | (0.74, 1.10) | 0.85 | (0.62,1.16) | -0.04 | (-0.11, 0.03) | |
| >=45 | 837 | 322 | 38.5 | 818 | 276 | 33.7 | 0.0452 | 0.88 | (0.77,<1.00) | 0.81 | (0.67,1.00) | -0.05 | (-0.09, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7332 |
| Normal (<30) | 452 | 168 | 37.2 | 456 | 147 | 32.2 | 0.1185 | 0.87 | (0.73, 1.04) | 0.80 | (0.61,1.06) | -0.05 | (-0.11, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 239 | 38.1 | 608 | 218 | 35.9 | 0.4103 | 0.94 | (0.81, 1.09) | 0.91 | (0.72,1.14) | -0.02 | (-0.08, 0.03) | |
| Macroalbuminuria (>300) | 189 | 84 | 44.4 | 207 | 88 | 42.5 | 0.6984 | 0.96 | (0.76, 1.20) | 0.92 | (0.62,1.38) | -0.02 | (-0.12, 0.08) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0324 |
| Low, moderate or high | 953 | 363 | 38.1 | 947 | 310 | 32.7 | 0.0147 | 0.86 | (0.76, 0.97) | 0.79 | (0.66,0.96) | -0.05 | (-0.10,-0.01) | |
| Very high | 315 | 128 | 40.6 | 325 | 144 | 44.3 | 0.3474 | 1.09 | (0.91, 1.31) | 1.16 | (0.85,1.59) | 0.04 | (-0.04, 0.11) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4799 |
| No | 161 | 68 | 42.2 | 168 | 71 | 42.3 | 0.9962 | 1.00 | (0.78, 1.29) | 1.00 | (0.65,1.55) | 0.00 | (-0.11, 0.11) | |
| Yes | 1113 | 425 | 38.2 | 1110 | 384 | 34.6 | 0.0785 | 0.91 | (0.81, 1.01) | 0.86 | (0.72,1.02) | -0.04 | (-0.08, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5718 |
| No | 62 | 26 | 41.9 | 72 | 31 | 43.1 | 0.8960 | 1.03 | (0.69, 1.52) | 1.05 | (0.53,2.08) | 0.01 | (-0.16, 0.18) | |
| Yes | 1212 | 467 | 38.5 | 1206 | 424 | 35.2 | 0.0855 | 0.91 | (0.82, 1.01) | 0.86 | (0.73,1.02) | -0.03 | (-0.07, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3642 |
| No | 46 | 18 | 39.1 | 57 | 16 | 28.1 | 0.2354 | 0.72 | (0.41, 1.24) | 0.61 | (0.27,1.39) | -0.11 | (-0.29, 0.07) | |
| Yes | 1228 | 475 | 38.7 | 1221 | 439 | 36.0 | 0.1630 | 0.93 | (0.84, 1.03) | 0.89 | (0.76,1.05) | -0.03 | (-0.07, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 5 Proportion of patients with severe adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 443 | 34.8 | 1278 | 400 | 31.3 | 0.0621 | 0.90 | (0.81, 1.01) | 0.85 | (0.72,1.01) | -0.03 | (-0.07, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.6528 |
| Male | 958 | 343 | 35.8 | 975 | 318 | 32.6 | 0.1395 | 0.91 | (0.80, 1.03) | 0.87 | (0.72,1.05) | -0.03 | (-0.07, 0.01) | |
| Female | 316 | 100 | 31.6 | 303 | 82 | 27.1 | 0.2109 | 0.86 | (0.67, 1.09) | 0.80 | (0.57,1.13) | -0.05 | (-0.12, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.9477 |
| <65 | 435 | 152 | 34.9 | 392 | 124 | 31.6 | 0.3135 | 0.91 | (0.75, 1.10) | 0.86 | (0.64,1.15) | -0.03 | (-0.10, 0.03) | |
| >=65 | 839 | 291 | 34.7 | 886 | 276 | 31.2 | 0.1185 | 0.90 | (0.78, 1.03) | 0.85 | (0.70,1.04) | -0.04 | (-0.08, 0.01) | |
| Region | | | | | | | | | | | | | | 0.9059 |
| North America | 161 | 74 | 46.0 | 159 | 66 | 41.5 | 0.4220 | 0.90 | (0.70, 1.16) | 0.83 | (0.54,1.30) | -0.04 | (-0.15, 0.06) | |
| Latin America | 420 | 141 | 33.6 | 440 | 142 | 32.3 | 0.6854 | 0.96 | (0.79, 1.16) | 0.94 | (0.71,1.25) | -0.01 | (-0.08, 0.05) | |
| Europe | 469 | 153 | 32.6 | 467 | 134 | 28.7 | 0.1924 | 0.88 | (0.72, 1.07) | 0.83 | (0.63,1.10) | -0.04 | (-0.10, 0.02) | |
| Asia | 174 | 62 | 35.6 | 165 | 49 | 29.7 | 0.2445 | 0.83 | (0.61, 1.13) | 0.76 | (0.48,1.20) | -0.06 | (-0.16, 0.04) | |
| Other | 50 | 13 | 26.0 | 47 | 9 | 19.1 | 0.4207 | 0.74 | (0.35, 1.56) | 0.67 | (0.26,1.77) | -0.07 | (-0.23, 0.10) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9632 |
| Diabetic | 694 | 258 | 37.2 | 698 | 233 | 33.4 | 0.1385 | 0.90 | (0.78, 1.04) | 0.85 | (0.68,1.06) | -0.04 | (-0.09, 0.01) | |
| Non-Diabetic | 580 | 185 | 31.9 | 580 | 167 | 28.8 | 0.2503 | 0.90 | (0.76, 1.08) | 0.86 | (0.67,1.11) | -0.03 | (-0.08, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1609 |
| <30 | 889 | 314 | 35.3 | 836 | 251 | 30.0 | 0.0192 | 0.85 | (0.74, 0.97) | 0.79 | (0.64,0.96) | -0.05 | (-0.10,-0.01) | |
| >=30 | 385 | 129 | 33.5 | 442 | 149 | 33.7 | 0.9506 | 1.01 | (0.83, 1.22) | 1.01 | (0.76,1.35) | 0.00 | (-0.06, 0.07) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3463 |
| <130 | 857 | 311 | 36.3 | 834 | 263 | 31.5 | 0.0390 | 0.87 | (0.76, 0.99) | 0.81 | (0.66,0.99) | -0.05 | (-0.09, 0.00) | |
| >=130 | 417 | 132 | 31.7 | 444 | 137 | 30.9 | 0.8005 | 0.97 | (0.80, 1.19) | 0.96 | (0.72,1.29) | -0.01 | (-0.07, 0.05) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2802 |
| <75 | 718 | 258 | 35.9 | 678 | 235 | 34.7 | 0.6191 | 0.96 | (0.84, 1.11) | 0.95 | (0.76,1.18) | -0.01 | (-0.06, 0.04) | |
| 75 to <85 | 348 | 111 | 31.9 | 382 | 107 | 28.0 | 0.2519 | 0.88 | (0.70, 1.10) | 0.83 | (0.60,1.14) | -0.04 | (-0.11, 0.03) | |
| >=85 | 208 | 74 | 35.6 | 218 | 58 | 26.6 | 0.0453 | 0.75 | (0.56,<1.00) | 0.66 | (0.43,0.99) | -0.09 | (-0.18, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 5 Proportion of patients with severe adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3657 |
| <30 | 89 | 37 | 41.6 | 115 | 53 | 46.1 | 0.5196 | 1.11 | (0.81, 1.52) | 1.20 | (0.69,2.10) | 0.05 | (-0.09, 0.18) | |
| 30 to <45 | 348 | 125 | 35.9 | 345 | 106 | 30.7 | 0.1469 | 0.86 | (0.69, 1.06) | 0.79 | (0.58,1.09) | -0.05 | (-0.12, 0.02) | |
| >=45 | 837 | 281 | 33.6 | 818 | 241 | 29.5 | 0.0720 | 0.88 | (0.76, 1.01) | 0.83 | (0.67,1.02) | -0.04 | (-0.09, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5481 |
| Normal (<30) | 452 | 133 | 29.4 | 456 | 117 | 25.7 | 0.2039 | 0.87 | (0.71, 1.08) | 0.83 | (0.62,1.11) | -0.04 | (-0.10, 0.02) | |
| Microalbuminuria (30 to <=300) | 627 | 228 | 36.4 | 608 | 195 | 32.1 | 0.1121 | 0.88 | (0.76, 1.03) | 0.83 | (0.65,1.05) | -0.04 | (-0.10, 0.01) | |
| Macroalbuminuria (>300) | 189 | 78 | 41.3 | 207 | 87 | 42.0 | 0.8784 | 1.02 | (0.81, 1.29) | 1.03 | (0.69,1.54) | 0.01 | (-0.09, 0.10) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2726 |
| Low, moderate or high | 953 | 312 | 32.7 | 947 | 270 | 28.5 | 0.0456 | 0.87 | (0.76,<1.00) | 0.82 | (0.67,1.00) | -0.04 | (-0.08, 0.00) | |
| Very high | 315 | 127 | 40.3 | 325 | 130 | 40.0 | 0.9347 | 0.99 | (0.82, 1.20) | 0.99 | (0.72,1.35) | 0.00 | (-0.08, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1447 |
| No | 161 | 58 | 36.0 | 168 | 66 | 39.3 | 0.5418 | 1.09 | (0.83, 1.44) | 1.15 | (0.74,1.80) | 0.03 | (-0.07, 0.14) | |
| Yes | 1113 | 385 | 34.6 | 1110 | 334 | 30.1 | 0.0233 | 0.87 | (0.77, 0.98) | 0.81 | (0.68,0.97) | -0.05 | (-0.08,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8768 |
| No | 62 | 26 | 41.9 | 72 | 28 | 38.9 | 0.7200 | 0.93 | (0.61, 1.40) | 0.88 | (0.44,1.76) | -0.03 | (-0.20, 0.14) | |
| Yes | 1212 | 417 | 34.4 | 1206 | 372 | 30.8 | 0.0619 | 0.90 | (0.80, 1.01) | 0.85 | (0.72,1.01) | -0.04 | (-0.07, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4306 |
| No | 46 | 11 | 23.9 | 57 | 9 | 15.8 | 0.3001 | 0.66 | (0.30, 1.46) | 0.60 | (0.22,1.59) | -0.08 | (-0.24, 0.07) | |
| Yes | 1228 | 432 | 35.2 | 1221 | 391 | 32.0 | 0.0983 | 0.91 | (0.81, 1.02) | 0.87 | (0.73,1.03) | -0.03 | (-0.07, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 228 | 17.9 | 1278 | 223 | 17.4 | 0.7671 | 0.98 | (0.82,1.15) | 0.97 | (0.79,1.19) | 0.00 | (-0.03, 0.03) | |
| Sex | | | | | | | | | | | | | | 0.6327 |
| Male | 958 | 178 | 18.6 | 975 | 180 | 18.5 | 0.9464 | 0.99 | (0.82,1.20) | 0.99 | (0.79,1.25) | 0.00 | (-0.04, 0.03) | |
| Female | 316 | 50 | 15.8 | 303 | 43 | 14.2 | 0.5701 | 0.90 | (0.62,1.31) | 0.88 | (0.57,1.37) | -0.02 | (-0.07, 0.04) | |
| Age [years] | | | | | | | | | | | | | | 0.7605 |
| <65 | 435 | 81 | 18.6 | 392 | 74 | 18.9 | 0.9247 | 1.01 | (0.76,1.35) | 1.02 | (0.72,1.44) | 0.00 | (-0.05, 0.06) | |
| >=65 | 839 | 147 | 17.5 | 886 | 149 | 16.8 | 0.6984 | 0.96 | (0.78,1.18) | 0.95 | (0.74,1.22) | -0.01 | (-0.04, 0.03) | |
| Region | | | | | | | | | | | | | | 0.1585 |
| North America | 161 | 49 | 30.4 | 159 | 47 | 29.6 | 0.8644 | 0.97 | (0.69,1.36) | 0.96 | (0.59,1.55) | -0.01 | (-0.11, 0.09) | |
| Latin America | 420 | 67 | 16.0 | 440 | 75 | 17.0 | 0.6661 | 1.07 | (0.79,1.44) | 1.08 | (0.75,1.55) | 0.01 | (-0.04, 0.06) | |
| Europe | 469 | 73 | 15.6 | 467 | 79 | 16.9 | 0.5751 | 1.09 | (0.81,1.45) | 1.10 | (0.78,1.56) | 0.01 | (-0.03, 0.06) | |
| Asia | 174 | 35 | 20.1 | 165 | 17 | 10.3 | 0.0122 | 0.51 | (0.30,0.88) | 0.46 | (0.24,0.85) | -0.10 | (-0.17,-0.02) | |
| Other | 50 | 4 | 8.0 | 47 | 5 | 10.6 | 0.6544 | 1.33 | (0.38,4.66) | 1.37 | (0.34,5.44) | 0.03 | (-0.09, 0.14) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7858 |
| Diabetic | 694 | 131 | 18.9 | 698 | 131 | 18.8 | 0.9588 | 0.99 | (0.80,1.24) | 0.99 | (0.76,1.30) | 0.00 | (-0.04, 0.04) | |
| Non-Diabetic | 580 | 97 | 16.7 | 580 | 92 | 15.9 | 0.6910 | 0.95 | (0.73,1.23) | 0.94 | (0.69,1.28) | -0.01 | (-0.05, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1706 |
| <30 | 889 | 160 | 18.0 | 836 | 134 | 16.0 | 0.2771 | 0.89 | (0.72,1.10) | 0.87 | (0.68,1.12) | -0.02 | (-0.06, 0.02) | |
| >=30 | 385 | 68 | 17.7 | 442 | 89 | 20.1 | 0.3656 | 1.14 | (0.86,1.52) | 1.18 | (0.83,1.67) | 0.02 | (-0.03, 0.08) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8962 |
| <130 | 857 | 157 | 18.3 | 834 | 148 | 17.7 | 0.7589 | 0.97 | (0.79,1.19) | 0.96 | (0.75,1.23) | -0.01 | (-0.04, 0.03) | |
| >=130 | 417 | 71 | 17.0 | 444 | 75 | 16.9 | 0.9581 | 0.99 | (0.74,1.33) | 0.99 | (0.69,1.41) | 0.00 | (-0.05, 0.05) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8251 |
| <75 | 718 | 131 | 18.2 | 678 | 126 | 18.6 | 0.8703 | 1.02 | (0.82,1.27) | 1.02 | (0.78,1.34) | 0.00 | (-0.04, 0.04) | |
| 75 to <85 | 348 | 55 | 15.8 | 382 | 58 | 15.2 | 0.8167 | 0.96 | (0.68,1.35) | 0.95 | (0.64,1.42) | -0.01 | (-0.06, 0.05) | |
| >=85 | 208 | 42 | 20.2 | 218 | 39 | 17.9 | 0.5450 | 0.89 | (0.60,1.31) | 0.86 | (0.53,1.40) | -0.02 | (-0.10, 0.05) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2389 |
| <30 | 89 | 18 | 20.2 | 115 | 33 | 28.7 | 0.1658 | 1.42 | (0.86,2.35) | 1.59 | (0.82,3.06) | 0.08 | (-0.03, 0.20) | |
| 30 to <45 | 348 | 61 | 17.5 | 345 | 51 | 14.8 | 0.3261 | 0.84 | (0.60,1.19) | 0.82 | (0.54,1.22) | -0.03 | (-0.08, 0.03) | |
| >=45 | 837 | 149 | 17.8 | 818 | 139 | 17.0 | 0.6643 | 0.95 | (0.77,1.18) | 0.95 | (0.73,1.22) | -0.01 | (-0.04, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7144 |
| Normal (<30) | 452 | 76 | 16.8 | 456 | 68 | 14.9 | 0.4328 | 0.89 | (0.66,1.20) | 0.87 | (0.61,1.24) | -0.02 | (-0.07, 0.03) | |
| Microalbuminuria (30 to <=300) | 627 | 107 | 17.1 | 608 | 108 | 17.8 | 0.7465 | 1.04 | (0.82,1.33) | 1.05 | (0.78,1.41) | 0.01 | (-0.04, 0.05) | |
| Macroalbuminuria (>300) | 189 | 44 | 23.3 | 207 | 46 | 22.2 | 0.8018 | 0.95 | (0.66,1.37) | 0.94 | (0.59,1.51) | -0.01 | (-0.09, 0.07) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1909 |
| Low, moderate or high | 953 | 165 | 17.3 | 947 | 149 | 15.7 | 0.3539 | 0.91 | (0.74,1.11) | 0.89 | (0.70,1.14) | -0.02 | (-0.05, 0.02) | |
| Very high | 315 | 62 | 19.7 | 325 | 74 | 22.8 | 0.3399 | 1.16 | (0.86,1.56) | 1.20 | (0.82,1.76) | 0.03 | (-0.03, 0.09) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2836 |
| No | 161 | 32 | 19.9 | 168 | 40 | 23.8 | 0.3883 | 1.20 | (0.79,1.81) | 1.26 | (0.75,2.13) | 0.04 | (-0.05, 0.13) | |
| Yes | 1113 | 196 | 17.6 | 1110 | 183 | 16.5 | 0.4812 | 0.94 | (0.78,1.12) | 0.92 | (0.74,1.15) | -0.01 | (-0.04, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6950 |
| No | 62 | 15 | 24.2 | 72 | 15 | 20.8 | 0.6417 | 0.86 | (0.46,1.62) | 0.82 | (0.37,1.86) | -0.03 | (-0.18, 0.11) | |
| Yes | 1212 | 213 | 17.6 | 1206 | 208 | 17.2 | 0.8320 | 0.98 | (0.82,1.17) | 0.98 | (0.79,1.21) | 0.00 | (-0.03, 0.03) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5066 |
| No | 46 | 6 | 13.0 | 57 | 5 | 8.8 | 0.4853 | 0.67 | (0.22,2.06) | 0.64 | (0.18,2.25) | -0.04 | (-0.16, 0.08) | |
| Yes | 1228 | 222 | 18.1 | 1221 | 218 | 17.9 | 0.8852 | 0.99 | (0.83,1.17) | 0.98 | (0.80,1.21) | 0.00 | (-0.03, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.3.2.2**

R.3.2.2 Adverse events leading to treatment discontinuation

Table R.3.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 271 | 21.3 | 1278 | 249 | 19.5 | 0.2622 | 0.92 | (0.79,1.07) | 0.90 | (0.74,1.09) | -0.02 | (-0.05, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.4313 |
| Male | 958 | 208 | 21.7 | 975 | 200 | 20.5 | 0.5183 | 0.94 | (0.80,1.12) | 0.93 | (0.75,1.16) | -0.01 | (-0.05, 0.02) | |
| Female | 316 | 63 | 19.9 | 303 | 49 | 16.2 | 0.2238 | 0.81 | (0.58,1.14) | 0.77 | (0.51,1.17) | -0.04 | (-0.10, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.7015 |
| <65 | 435 | 82 | 18.9 | 392 | 64 | 16.3 | 0.3418 | 0.87 | (0.64,1.17) | 0.84 | (0.59,1.20) | -0.03 | (-0.08, 0.03) | |
| >=65 | 839 | 189 | 22.5 | 886 | 185 | 20.9 | 0.4069 | 0.93 | (0.77,1.11) | 0.91 | (0.72,1.14) | -0.02 | (-0.06, 0.02) | |
| Region | | | | | | | | | | | | | | 0.3143 |
| North America | 161 | 45 | 28.0 | 159 | 36 | 22.6 | 0.2748 | 0.81 | (0.55,1.18) | 0.75 | (0.45,1.25) | -0.05 | (-0.15, 0.04) | |
| Latin America | 420 | 87 | 20.7 | 440 | 82 | 18.6 | 0.4433 | 0.90 | (0.69,1.18) | 0.88 | (0.63,1.23) | -0.02 | (-0.07, 0.03) | |
| Europe | 469 | 105 | 22.4 | 467 | 102 | 21.8 | 0.8404 | 0.98 | (0.77,1.24) | 0.97 | (0.71,1.32) | -0.01 | (-0.06, 0.05) | |
| Asia | 174 | 22 | 12.6 | 165 | 25 | 15.2 | 0.5042 | 1.20 | (0.70,2.04) | 1.23 | (0.67,2.29) | 0.03 | (-0.05, 0.10) | |
| Other | 50 | 12 | 24.0 | 47 | 4 | 8.5 | 0.0400 | 0.35 | (0.12,1.02) | 0.29 | (0.09,0.99) | -0.15 | (-0.30,-0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9120 |
| Diabetic | 694 | 153 | 22.0 | 698 | 142 | 20.3 | 0.4371 | 0.92 | (0.75,1.13) | 0.90 | (0.70,1.17) | -0.02 | (-0.06, 0.03) | |
| Non-Diabetic | 580 | 118 | 20.3 | 580 | 107 | 18.4 | 0.4140 | 0.91 | (0.72,1.15) | 0.89 | (0.66,1.19) | -0.02 | (-0.06, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2573 |
| <30 | 889 | 195 | 21.9 | 836 | 158 | 18.9 | 0.1184 | 0.86 | (0.71,1.04) | 0.83 | (0.66,1.05) | -0.03 | (-0.07, 0.01) | |
| >=30 | 385 | 76 | 19.7 | 442 | 91 | 20.6 | 0.7619 | 1.04 | (0.79,1.37) | 1.05 | (0.75,1.48) | 0.01 | (-0.05, 0.06) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9430 |
| <130 | 857 | 193 | 22.5 | 834 | 172 | 20.6 | 0.3432 | 0.92 | (0.76,1.10) | 0.89 | (0.71,1.13) | -0.02 | (-0.06, 0.02) | |
| >=130 | 417 | 78 | 18.7 | 444 | 77 | 17.3 | 0.6030 | 0.93 | (0.70,1.23) | 0.91 | (0.64,1.29) | -0.01 | (-0.07, 0.04) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4336 |
| <75 | 718 | 173 | 24.1 | 678 | 151 | 22.3 | 0.4199 | 0.92 | (0.76,1.12) | 0.90 | (0.70,1.16) | -0.02 | (-0.06, 0.03) | |
| 75 to <85 | 348 | 58 | 16.7 | 382 | 67 | 17.5 | 0.7546 | 1.05 | (0.76,1.45) | 1.06 | (0.72,1.56) | 0.01 | (-0.05, 0.06) | |
| >=85 | 208 | 40 | 19.2 | 218 | 31 | 14.2 | 0.1654 | 0.74 | (0.48,1.14) | 0.70 | (0.42,1.16) | -0.05 | (-0.12, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6996 |
| <30 | 89 | 26 | 29.2 | 115 | 36 | 31.3 | 0.7475 | 1.07 | (0.70,1.63) | 1.10 | (0.60,2.02) | 0.02 | (-0.11, 0.15) | |
| 30 to <45 | 348 | 86 | 24.7 | 345 | 77 | 22.3 | 0.4576 | 0.90 | (0.69,1.18) | 0.88 | (0.62,1.24) | -0.02 | (-0.09, 0.04) | |
| >=45 | 837 | 159 | 19.0 | 818 | 136 | 16.6 | 0.2077 | 0.88 | (0.71,1.08) | 0.85 | (0.66,1.09) | -0.02 | (-0.06, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.0751 |
| Normal (<30) | 452 | 87 | 19.2 | 456 | 77 | 16.9 | 0.3550 | 0.88 | (0.66,1.16) | 0.85 | (0.61,1.20) | -0.02 | (-0.07, 0.03) | |
| Microalbuminuria (30 to <=300) | 627 | 142 | 22.6 | 608 | 114 | 18.8 | 0.0912 | 0.83 | (0.66,1.03) | 0.79 | (0.60,1.04) | -0.04 | (-0.08, 0.01) | |
| Macroalbuminuria (>300) | 189 | 39 | 20.6 | 207 | 57 | 27.5 | 0.1095 | 1.33 | (0.93,1.91) | 1.46 | (0.92,2.33) | 0.07 | (-0.01, 0.15) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2313 |
| Low, moderate or high | 953 | 185 | 19.4 | 947 | 159 | 16.8 | 0.1377 | 0.86 | (0.71,1.05) | 0.84 | (0.66,1.06) | -0.03 | (-0.06, 0.01) | |
| Very high | 315 | 83 | 26.3 | 325 | 90 | 27.7 | 0.7021 | 1.05 | (0.81,1.36) | 1.07 | (0.76,1.52) | 0.01 | (-0.06, 0.08) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9958 |
| No | 161 | 43 | 26.7 | 168 | 41 | 24.4 | 0.6320 | 0.91 | (0.63,1.32) | 0.89 | (0.54,1.45) | -0.02 | (-0.12, 0.07) | |
| Yes | 1113 | 228 | 20.5 | 1110 | 208 | 18.7 | 0.2998 | 0.91 | (0.77,1.08) | 0.90 | (0.73,1.10) | -0.02 | (-0.05, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8302 |
| No | 62 | 18 | 29.0 | 72 | 18 | 25.0 | 0.5996 | 0.86 | (0.49,1.50) | 0.81 | (0.38,1.75) | -0.04 | (-0.19, 0.11) | |
| Yes | 1212 | 253 | 20.9 | 1206 | 231 | 19.2 | 0.2905 | 0.92 | (0.78,1.08) | 0.90 | (0.74,1.10) | -0.02 | (-0.05, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.0384 |
| No | 46 | 12 | 26.1 | 57 | 5 | 8.8 | 0.0186 | 0.34 | (0.13,0.89) | 0.27 | (0.09,0.84) | -0.17 | (-0.32,-0.03) | |
| Yes | 1228 | 259 | 21.1 | 1221 | 244 | 20.0 | 0.4975 | 0.95 | (0.81,1.11) | 0.93 | (0.77,1.14) | -0.01 | (-0.04, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Number of patients | 1274 (100.0) | | | 1278 (100.0) | | |
| Total with adverse events | 271 ( 21.3) | 1652.09 | 16.40 | 249 ( 19.5) | 1676.52 | 14.85 |
| Cardiac disorders | 105 ( 8.2) | 1723.73 | 6.09 | 90 ( 7.0) | 1753.83 | 5.13 |
| Cardiac failure | 59 ( 4.6) | 1729.38 | 3.41 | 50 ( 3.9) | 1762.06 | 2.84 |
| Cardiac failure acute | 6 ( 0.5) | 1750.09 | 0.34 | 5 ( 0.4) | 1771.14 | 0.28 |
| Cardiac failure congestive | 6 ( 0.5) | 1750.60 | 0.34 | 4 ( 0.3) | 1772.04 | 0.23 |
| Cardiac arrest | 5 ( 0.4) | 1751.73 | 0.29 | 6 ( 0.5) | 1773.62 | 0.34 |
| Acute myocardial infarction | 5 ( 0.4) | 1751.64 | 0.29 | 4 ( 0.3) | 1773.67 | 0.23 |
| Myocardial infarction | 5 ( 0.4) | 1751.68 | 0.29 | 4 ( 0.3) | 1773.67 | 0.23 |
| Cardio-respiratory arrest | 3 ( 0.2) | 1751.54 | 0.17 | 0 | 1773.67 | 0 |
| Cardiogenic shock | 3 ( 0.2) | 1751.77 | 0.17 | 3 ( 0.2) | 1773.65 | 0.17 |
| Cardiac failure chronic | 2 ( 0.2) | 1751.64 | 0.11 | 1 ( 0.1) | 1773.65 | 0.06 |
| Ventricular arrhythmia | 2 ( 0.2) | 1751.76 | 0.11 | 0 | 1773.67 | 0 |
| Ventricular fibrillation | 1 ( 0.1) | 1751.76 | 0.06 | 2 ( 0.2) | 1773.67 | 0.11 |
| Arrhythmia | 1 ( 0.1) | 1750.58 | 0.06 | 0 | 1773.67 | 0 |
| Arrhythmic storm | 1 ( 0.1) | 1751.77 | 0.06 | 0 | 1773.67 | 0 |
| Bradycardia | 1 ( 0.1) | 1751.06 | 0.06 | 0 | 1773.67 | 0 |
| Cardiopulmonary failure | 1 ( 0.1) | 1751.77 | 0.06 | 1 ( 0.1) | 1773.67 | 0.06 |
| Congestive cardiomyopathy | 1 ( 0.1) | 1751.77 | 0.06 | 0 | 1773.67 | 0 |
| Coronary artery disease | 1 ( 0.1) | 1751.77 | 0.06 | 0 | 1773.67 | 0 |
| Left ventricular dysfunction | 1 ( 0.1) | 1751.77 | 0.06 | 0 | 1773.67 | 0 |
| Ventricular tachycardia | 1 ( 0.1) | 1751.49 | 0.06 | 1 ( 0.1) | 1773.63 | 0.06 |
| Acute left ventricular failure | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.65 | 0.06 |
| Angina unstable | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.65 | 0.06 |
| Aortic valve incompetence | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.51 | 0.06 |
| Atrial tachycardia | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.49 | 0.06 |
| Cardiac tamponade | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |
| Chronic left ventricular failure | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.27 | 0.06 |
| Ischaemic cardiomyopathy | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |
| Mitral valve incompetence | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.64 | 0.06 |
| Paroxysmal atrioventricular block | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.57 | 0.06 |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.3.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| General disorders and administration site conditions | 41 ( 3.2) | 1749.72 | 2.34 | 31 ( 2.4) | 1767.10 | 1.75 |
| Death | 19 ( 1.5) | 1751.77 | 1.08 | 11 ( 0.9) | 1773.66 | 0.62 |
| Sudden cardiac death | 8 ( 0.6) | 1751.77 | 0.46 | 5 ( 0.4) | 1773.67 | 0.28 |
| Cardiac death | 6 ( 0.5) | 1751.77 | 0.34 | 4 ( 0.3) | 1773.67 | 0.23 |
| Sudden death | 4 ( 0.3) | 1751.77 | 0.23 | 3 ( 0.2) | 1773.67 | 0.17 |
| Malaise | 2 ( 0.2) | 1750.49 | 0.11 | 1 ( 0.1) | 1773.14 | 0.06 |
| Asthenia | 1 ( 0.1) | 1751.01 | 0.06 | 2 ( 0.2) | 1770.81 | 0.11 |
| Fatigue | 0 | 1751.77 | 0 | 2 ( 0.2) | 1772.25 | 0.11 |
| Multiple organ dysfunction syndrome | 1 ( 0.1) | 1751.76 | 0.06 | 1 ( 0.1) | 1773.67 | 0.06 |
| Pain | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.89 | 0.06 |
| Peripheral swelling | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.72 | 0.06 |
| Infections and infestations | 19 ( 1.5) | 1744.56 | 1.09 | 27 ( 2.1) | 1765.33 | 1.53 |
| Pneumonia | 6 ( 0.5) | 1750.87 | 0.34 | 3 ( 0.2) | 1773.56 | 0.17 |
| Septic shock | 3 ( 0.2) | 1751.72 | 0.17 | 6 ( 0.5) | 1772.27 | 0.34 |
| Sepsis | 1 ( 0.1) | 1751.77 | 0.06 | 5 ( 0.4) | 1773.46 | 0.28 |
| Urinary tract infection | 4 ( 0.3) | 1747.04 | 0.23 | 5 ( 0.4) | 1770.39 | 0.28 |
| Pneumonia aspiration | 0 | 1751.77 | 0 | 2 ( 0.2) | 1773.32 | 0.11 |
| Appendicitis | 1 ( 0.1) | 1751.64 | 0.06 | 0 | 1773.67 | 0 |
| Asymptomatic bacteriuria | 1 ( 0.1) | 1751.61 | 0.06 | 0 | 1773.67 | 0 |
| Endocarditis | 1 ( 0.1) | 1751.75 | 0.06 | 0 | 1773.67 | 0 |
| Gastroenteritis | 1 ( 0.1) | 1751.26 | 0.06 | 1 ( 0.1) | 1773.65 | 0.06 |
| Localised infection | 1 ( 0.1) | 1751.04 | 0.06 | 0 | 1773.67 | 0 |
| Device related infection | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.60 | 0.06 |
| Escherichia bacteraemia | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.50 | 0.06 |
| Fournier’s gangrene | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.50 | 0.06 |
| Spontaneous bacterial peritonitis | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.64 | 0.06 |
| Urosepsis | 0 | 1751.77 | 0 | 1 ( 0.1) | 1771.76 | 0.06 |
| Vulvovaginal mycotic infection | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.04 | 0.06 |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.3.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Renal and urinary disorders | 22 ( 1.7) | 1739.70 | 1.26 | 20 ( 1.6) | 1756.27 | 1.14 |
| Renal impairment | 3 ( 0.2) | 1749.49 | 0.17 | 9 ( 0.7) | 1762.80 | 0.51 |
| Acute kidney injury | 6 ( 0.5) | 1750.71 | 0.34 | 2 ( 0.2) | 1773.28 | 0.11 |
| Renal failure | 5 ( 0.4) | 1750.21 | 0.29 | 3 ( 0.2) | 1771.00 | 0.17 |
| Chronic kidney disease | 4 ( 0.3) | 1748.48 | 0.23 | 4 ( 0.3) | 1770.31 | 0.23 |
| Dysuria | 1 ( 0.1) | 1751.11 | 0.06 | 0 | 1773.67 | 0 |
| End stage renal disease | 1 ( 0.1) | 1750.26 | 0.06 | 0 | 1773.67 | 0 |
| Pollakiuria | 1 ( 0.1) | 1750.58 | 0.06 | 1 ( 0.1) | 1773.57 | 0.06 |
| Urinary incontinence | 1 ( 0.1) | 1751.22 | 0.06 | 0 | 1773.67 | 0 |
| Nephropathy | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |
| Nervous system disorders | 14 ( 1.1) | 1744.08 | 0.80 | 13 ( 1.0) | 1768.65 | 0.74 |
| Ischaemic stroke | 5 ( 0.4) | 1749.94 | 0.29 | 1 ( 0.1) | 1773.67 | 0.06 |
| Cerebrovascular accident | 3 ( 0.2) | 1751.73 | 0.17 | 3 ( 0.2) | 1772.99 | 0.17 |
| Dementia | 2 ( 0.2) | 1750.80 | 0.11 | 0 | 1773.67 | 0 |
| Dizziness | 2 ( 0.2) | 1748.88 | 0.11 | 0 | 1773.67 | 0 |
| Cognitive disorder | 0 | 1751.77 | 0 | 2 ( 0.2) | 1772.66 | 0.11 |
| Haemorrhagic stroke | 0 | 1751.77 | 0 | 2 ( 0.2) | 1773.67 | 0.11 |
| Syncope | 0 | 1751.77 | 0 | 2 ( 0.2) | 1771.05 | 0.11 |
| Headache | 1 ( 0.1) | 1751.09 | 0.06 | 0 | 1773.67 | 0 |
| Memory impairment | 1 ( 0.1) | 1750.48 | 0.06 | 0 | 1773.67 | 0 |
| Cerebral infarction | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.66 | 0.06 |
| Parkinson’s disease | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.12 | 0.06 |
| Seizure | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.55 | 0.06 |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.3.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Gastrointestinal disorders | 12 ( 0.9) | 1742.80 | 0.69 | 10 ( 0.8) | 1767.77 | 0.57 |
| Dyspepsia | 2 ( 0.2) | 1751.00 | 0.11 | 0 | 1773.67 | 0 |
| Gastrointestinal haemorrhage | 2 ( 0.2) | 1751.44 | 0.11 | 1 ( 0.1) | 1773.62 | 0.06 |
| Constipation | 0 | 1751.77 | 0 | 2 ( 0.2) | 1772.12 | 0.11 |
| Nausea | 1 ( 0.1) | 1750.66 | 0.06 | 2 ( 0.2) | 1772.56 | 0.11 |
| Abdominal distension | 1 ( 0.1) | 1751.12 | 0.06 | 0 | 1773.67 | 0 |
| Abdominal pain upper | 1 ( 0.1) | 1749.71 | 0.06 | 1 ( 0.1) | 1772.93 | 0.06 |
| Dry mouth | 1 ( 0.1) | 1751.05 | 0.06 | 0 | 1773.67 | 0 |
| Flatulence | 1 ( 0.1) | 1750.06 | 0.06 | 0 | 1773.67 | 0 |
| Gastritis | 1 ( 0.1) | 1750.19 | 0.06 | 0 | 1773.67 | 0 |
| Intestinal ischaemia | 1 ( 0.1) | 1751.76 | 0.06 | 0 | 1773.67 | 0 |
| Obstructive pancreatitis | 1 ( 0.1) | 1751.72 | 0.06 | 0 | 1773.67 | 0 |
| Gastric ulcer | 0 | 1751.77 | 0 | 1 ( 0.1) | 1771.24 | 0.06 |
| Pancreatitis acute | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |
| Rectal haemorrhage | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.66 | 0.06 |
| Upper gastrointestinal haemorrhage | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |
| Vascular disorders | 9 ( 0.7) | 1746.06 | 0.52 | 12 ( 0.9) | 1764.03 | 0.68 |
| Hypotension | 3 ( 0.2) | 1748.86 | 0.17 | 6 ( 0.5) | 1766.05 | 0.34 |
| Circulatory collapse | 2 ( 0.2) | 1751.77 | 0.11 | 0 | 1773.67 | 0 |
| Leriche syndrome | 0 | 1751.77 | 0 | 2 ( 0.2) | 1772.90 | 0.11 |
| Peripheral arterial occlusive disease | 1 ( 0.1) | 1750.90 | 0.06 | 2 ( 0.2) | 1772.61 | 0.11 |
| Giant cell arteritis | 1 ( 0.1) | 1749.88 | 0.06 | 0 | 1773.67 | 0 |
| Peripheral embolism | 1 ( 0.1) | 1751.76 | 0.06 | 0 | 1773.67 | 0 |
| Peripheral ischaemia | 1 ( 0.1) | 1751.72 | 0.06 | 1 ( 0.1) | 1773.51 | 0.06 |
| Dry gangrene | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.65 | 0.06 |
| Metabolism and nutrition disorders | 11 ( 0.9) | 1746.12 | 0.63 | 10 ( 0.8) | 1768.58 | 0.57 |
| Hypoglycaemia | 3 ( 0.2) | 1750.64 | 0.17 | 3 ( 0.2) | 1771.86 | 0.17 |
| Dehydration | 0 | 1751.77 | 0 | 3 ( 0.2) | 1771.41 | 0.17 |
| Diabetes mellitus | 2 ( 0.2) | 1750.81 | 0.11 | 0 | 1773.67 | 0 |
| Hyperkalaemia | 2 ( 0.2) | 1750.87 | 0.11 | 0 | 1773.67 | 0 |
| Cachexia | 1 ( 0.1) | 1751.74 | 0.06 | 0 | 1773.67 | 0 |
| Diabetes mellitus inadequate control | 1 ( 0.1) | 1750.20 | 0.06 | 0 | 1773.67 | 0 |
| Gout | 1 ( 0.1) | 1751.19 | 0.06 | 0 | 1773.67 | 0 |
| Type 2 diabetes mellitus | 1 ( 0.1) | 1751.28 | 0.06 | 1 ( 0.1) | 1773.47 | 0.06 |
| Decreased appetite | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.02 | 0.06 |
| Hypernatraemia | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.51 | 0.06 |
| Metabolic acidosis | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.3.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Investigations | 8 ( 0.6) | 1746.14 | 0.46 | 3 ( 0.2) | 1771.88 | 0.17 |
| Glomerular filtration rate decreased | 4 ( 0.3) | 1748.87 | 0.23 | 0 | 1773.67 | 0 |
| Hepatic enzyme increased | 2 ( 0.2) | 1750.69 | 0.11 | 0 | 1773.67 | 0 |
| Gamma-glutamyltransferase increased | 1 ( 0.1) | 1751.45 | 0.06 | 0 | 1773.67 | 0 |
| Urine ketone body present | 1 ( 0.1) | 1750.43 | 0.06 | 0 | 1773.67 | 0 |
| Aspartate aminotransferase increased | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.65 | 0.06 |
| Blood creatine phosphokinase increased | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.17 | 0.06 |
| Weight decreased | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.41 | 0.06 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 8 ( 0.6) | 1749.63 | 0.46 | 8 ( 0.6) | 1767.85 | 0.45 |
| Adenocarcinoma pancreas | 2 ( 0.2) | 1750.78 | 0.11 | 0 | 1773.67 | 0 |
| Lung neoplasm malignant | 2 ( 0.2) | 1751.50 | 0.11 | 0 | 1773.67 | 0 |
| Pancreatic carcinoma | 2 ( 0.2) | 1751.39 | 0.11 | 0 | 1773.67 | 0 |
| Monoclonal gammopathy | 1 ( 0.1) | 1751.45 | 0.06 | 0 | 1773.67 | 0 |
| Oesophageal carcinoma | 1 ( 0.1) | 1751.58 | 0.06 | 0 | 1773.67 | 0 |
| Abdominal neoplasm | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.48 | 0.06 |
| Bladder neoplasm | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.29 | 0.06 |
| Diffuse large B-cell lymphoma | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.76 | 0.06 |
| Lung neoplasm | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.45 | 0.06 |
| Pancreatic carcinoma metastatic | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.36 | 0.06 |
| Prostate cancer metastatic | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.52 | 0.06 |
| Renal cancer metastatic | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.25 | 0.06 |
| Ureteric cancer | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.47 | 0.06 |
| Injury, poisoning and procedural complications | 3 ( 0.2) | 1751.34 | 0.17 | 8 ( 0.6) | 1771.53 | 0.45 |
| Fall | 1 ( 0.1) | 1751.61 | 0.06 | 2 ( 0.2) | 1773.33 | 0.11 |
| Multiple injuries | 1 ( 0.1) | 1751.73 | 0.06 | 0 | 1773.67 | 0 |
| Upper limb fracture | 1 ( 0.1) | 1751.53 | 0.06 | 0 | 1773.67 | 0 |
| Fracture | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |
| Hip fracture | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.49 | 0.06 |
| Splenic rupture | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.67 | 0.06 |
| Subdural haematoma | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.65 | 0.06 |
| Traumatic fracture | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.08 | 0.06 |
| Traumatic intracranial haemorrhage | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.66 | 0.06 |

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MedDRA version: 25.0

Table R.3.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | 6 ( 0.5) | 1744.59 | 0.34 | 7 ( 0.5) | 1769.32 | 0.40 |
| Pruritus | 2 ( 0.2) | 1748.65 | 0.11 | 2 ( 0.2) | 1771.92 | 0.11 |
| Diabetic foot | 0 | 1751.77 | 0 | 2 ( 0.2) | 1773.33 | 0.11 |
| Pruritus allergic | 1 ( 0.1) | 1750.27 | 0.06 | 1 ( 0.1) | 1772.56 | 0.06 |
| Psoriasis | 1 ( 0.1) | 1751.49 | 0.06 | 0 | 1773.67 | 0 |
| Rash | 1 ( 0.1) | 1751.65 | 0.06 | 1 ( 0.1) | 1772.66 | 0.06 |
| Rash erythematous | 1 ( 0.1) | 1749.61 | 0.06 | 0 | 1773.67 | 0 |
| Skin ulcer | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.55 | 0.06 |
| Respiratory, thoracic and mediastinal disorders | 6 ( 0.5) | 1751.37 | 0.34 | 4 ( 0.3) | 1773.56 | 0.23 |
| Chronic obstructive pulmonary disease | 2 ( 0.2) | 1751.56 | 0.11 | 0 | 1773.67 | 0 |
| Acute pulmonary oedema | 1 ( 0.1) | 1751.77 | 0.06 | 1 ( 0.1) | 1773.56 | 0.06 |
| Idiopathic pulmonary fibrosis | 1 ( 0.1) | 1751.75 | 0.06 | 0 | 1773.67 | 0 |
| Pneumonitis | 1 ( 0.1) | 1751.77 | 0.06 | 0 | 1773.67 | 0 |
| Pulmonary embolism | 1 ( 0.1) | 1751.59 | 0.06 | 1 ( 0.1) | 1773.67 | 0.06 |
| Dyspnoea | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |
| Respiratory arrest | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |
| Psychiatric disorders | 3 ( 0.2) | 1748.31 | 0.17 | 3 ( 0.2) | 1770.25 | 0.17 |
| Anxiety | 1 ( 0.1) | 1749.57 | 0.06 | 0 | 1773.67 | 0 |
| Insomnia | 1 ( 0.1) | 1750.63 | 0.06 | 0 | 1773.67 | 0 |
| Mental status changes | 1 ( 0.1) | 1751.64 | 0.06 | 0 | 1773.67 | 0 |
| Completed suicide | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |
| Mood altered | 0 | 1751.77 | 0 | 1 ( 0.1) | 1771.81 | 0.06 |
| Poor quality sleep | 0 | 1751.77 | 0 | 1 ( 0.1) | 1772.11 | 0.06 |
| Musculoskeletal and connective tissue disorders | 1 ( 0.1) | 1751.06 | 0.06 | 2 ( 0.2) | 1771.88 | 0.11 |
| Pain in extremity | 1 ( 0.1) | 1751.06 | 0.06 | 1 ( 0.1) | 1772.49 | 0.06 |
| Back pain | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.06 | 0.06 |
| Eye disorders | 1 ( 0.1) | 1749.90 | 0.06 | 0 | 1773.67 | 0 |
| Ocular hyperaemia | 1 ( 0.1) | 1749.90 | 0.06 | 0 | 1773.67 | 0 |
| Hepatobiliary disorders | 1 ( 0.1) | 1751.73 | 0.06 | 1 ( 0.1) | 1773.66 | 0.06 |
| Hepatic mass | 1 ( 0.1) | 1751.73 | 0.06 | 0 | 1773.67 | 0 |
| Hepatorenal syndrome | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.66 | 0.06 |

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Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.3.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Reproductive system and breast disorders | 1 ( 0.1) | 1750.89 | 0.06 | 0 | 1773.67 | 0 |
| Erectile dysfunction | 1 ( 0.1) | 1750.89 | 0.06 | 0 | 1773.67 | 0 |
| Surgical and medical procedures | 1 ( 0.1) | 1751.58 | 0.06 | 1 ( 0.1) | 1773.67 | 0.06 |
| Hip arthroplasty | 1 ( 0.1) | 1751.58 | 0.06 | 0 | 1773.67 | 0 |
| Euthanasia | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.67 | 0.06 |
| Blood and lymphatic system disorders | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.18 | 0.06 |
| Pancytopenia | 0 | 1751.77 | 0 | 1 ( 0.1) | 1773.18 | 0.06 |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

**R.3.2.3**

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 9 | 0.7 | 1278 | 13 | 1.0 | 0.3958 | 1.44 ( 0.62, | 3.36) | 1.44 ( 0.62, | 3.39) | 0.00 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | 0.3602 |
| Male | 958 | 6 | 0.6 | 975 | 11 | 1.1 | 0.2373 | 1.80 ( 0.67, | 4.85) | 1.81 ( 0.67, | 4.92) | 0.01 ( 0.00, 0.01) | |
| Female | 316 | 3 | 0.9 | 303 | 2 | 0.7 | 0.6877 | 0.70 ( 0.12, | 4.13) | 0.69 ( 0.12, | 4.18) | 0.00 (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | 0.4361 |
| <65 | 435 | 3 | 0.7 | 392 | 6 | 1.5 | 0.2445 | 2.22 ( 0.56, | 8.81) | 2.24 ( 0.56, | 9.01) | 0.01 (-0.01, 0.02) | |
| >=65 | 839 | 6 | 0.7 | 886 | 7 | 0.8 | 0.8573 | 1.10 ( 0.37, | 3.27) | 1.11 ( 0.37, | 3.30) | 0.00 (-0.01, 0.01) | |
| Region | | | | | | | | | | | | | 0.9099 |
| North America | 161 | 1 | 0.6 | 159 | 1 | 0.6 | 0.9929 | 1.01 ( 0.06, | 16.05) | 1.01 ( 0.06, | 16.33) | 0.00 (-0.02, 0.02) | |
| Latin America | 420 | 3 | 0.7 | 440 | 6 | 1.4 | 0.3496 | 1.91 ( 0.48, | 7.58) | 1.92 ( 0.48, | 7.73) | 0.01 (-0.01, 0.02) | |
| Europe | 469 | 4 | 0.9 | 467 | 6 | 1.3 | 0.5204 | 1.51 ( 0.43, | 5.30) | 1.51 ( 0.42, | 5.40) | 0.00 (-0.01, 0.02) | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | 0.9789 | 1.05 ( 0.02, | 52.82) | 1.05 ( 0.02, | 53.44) | 0.00 (-0.01, 0.01) | |
| Other | 50 | 1 | 2.0 | 47 | 0 | 0 | 0.5020 | 0.35 ( 0.01, | 8.48) | 0.35 ( 0.01, | 8.74) | -0.02 (-0.07, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.7876 |
| Diabetic | 694 | 8 | 1.2 | 698 | 12 | 1.7 | 0.3746 | 1.49 ( 0.61, | 3.63) | 1.50 ( 0.61, | 3.69) | 0.01 (-0.01, 0.02) | |
| Non-Diabetic | 580 | 1 | 0.2 | 580 | 1 | 0.2 | 1.0000 | 1.00 ( 0.06, | 15.95) | 1.00 ( 0.06, | 16.03) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.1319 |
| <30 | 889 | 3 | 0.3 | 836 | 8 | 1.0 | 0.1062 | 2.84 ( 0.75, | 10.65) | 2.85 ( 0.75, | 10.79) | 0.01 ( 0.00, 0.01) | |
| >=30 | 385 | 6 | 1.6 | 442 | 5 | 1.1 | 0.5927 | 0.73 ( 0.22, | 2.36) | 0.72 ( 0.22, | 2.39) | 0.00 (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.9807 |
| <130 | 857 | 5 | 0.6 | 834 | 7 | 0.8 | 0.5308 | 1.44 ( 0.46, | 4.51) | 1.44 ( 0.46, | 4.56) | 0.00 (-0.01, 0.01) | |
| >=130 | 417 | 4 | 1.0 | 444 | 6 | 1.4 | 0.5915 | 1.41 ( 0.40, | 4.96) | 1.41 ( 0.40, | 5.05) | 0.00 (-0.01, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.2663 |
| <75 | 718 | 3 | 0.4 | 678 | 8 | 1.2 | 0.1075 | 2.82 ( 0.75, | 10.60) | 2.85 ( 0.75, | 10.77) | 0.01 ( 0.00, 0.02) | |
| 75 to <85 | 348 | 2 | 0.6 | 382 | 3 | 0.8 | 0.7304 | 1.37 ( 0.23, | 8.13) | 1.37 ( 0.23, | 8.24) | 0.00 (-0.01, 0.01) | |
| >=85 | 208 | 4 | 1.9 | 218 | 2 | 0.9 | 0.3786 | 0.48 ( 0.09, | 2.58) | 0.47 ( 0.09, | 2.61) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.9500 |
| <30 | 89 | 0 | 0 | 115 | 1 | 0.9 | 0.5923 | 2.33 ( 0.10, 56.46) | 2.34 ( 0.09, 58.25) | 0.01 (-0.02, 0.03) | |
| 30 to <45 | 348 | 3 | 0.9 | 345 | 4 | 1.2 | 0.6955 | 1.34 ( 0.30, 5.96) | 1.35 ( 0.30, 6.07) | 0.00 (-0.01, 0.02) | |
| >=45 | 837 | 6 | 0.7 | 818 | 8 | 1.0 | 0.5619 | 1.36 ( 0.48, 3.91) | 1.37 ( 0.47, 3.96) | 0.00 (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 2 | 0.4 | 456 | 3 | 0.7 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 4 | 0.6 | 608 | 5 | 0.8 | | | | | |
| Macroalbuminuria (>300) | 189 | 3 | 1.6 | 207 | 5 | 2.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.2763 |
| Low, moderate or high | 953 | 5 | 0.5 | 947 | 10 | 1.1 | 0.1907 | 2.01 ( 0.69, 5.87) | 2.02 ( 0.69, 5.94) | 0.01 ( 0.00, 0.01) | |
| Very high | 315 | 4 | 1.3 | 325 | 3 | 0.9 | 0.6733 | 0.73 ( 0.16, 3.22) | 0.72 ( 0.16, 3.26) | 0.00 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.1590 |
| No | 161 | 2 | 1.2 | 168 | 0 | 0 | 0.2313 | 0.19 (<0.01, 3.96) | 0.19 (<0.01, 3.97) | -0.01 (-0.03, 0.01) | |
| Yes | 1113 | 7 | 0.6 | 1110 | 13 | 1.2 | 0.1758 | 1.86 ( 0.75, 4.65) | 1.87 ( 0.74, 4.71) | 0.01 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.7043 |
| No | 62 | 1 | 1.6 | 72 | 1 | 1.4 | 0.9151 | 0.86 ( 0.05, 13.48) | 0.86 ( 0.05, 14.03) | 0.00 (-0.04, 0.04) | |
| Yes | 1212 | 8 | 0.7 | 1206 | 12 | 1.0 | 0.3632 | 1.51 ( 0.62, 3.67) | 1.51 ( 0.62, 3.71) | 0.00 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.2845 |
| No | 46 | 1 | 2.2 | 57 | 0 | 0 | 0.3852 | 0.27 ( 0.01, 6.48) | 0.26 ( 0.01, 6.63) | -0.02 (-0.08, 0.03) | |
| Yes | 1228 | 8 | 0.7 | 1221 | 13 | 1.1 | 0.2674 | 1.63 ( 0.68, 3.93) | 1.64 ( 0.68, 3.97) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 69 | 5.4 | 1278 | 70 | 5.5 | 0.9456 | 1.01 ( 0.73, 1.40) | 1.01 ( 0.72, 1.42) | 0.00 (-0.02, 0.02) | |
| Sex | | | | | | | | | | | 0.2195 |
| Male | 958 | 53 | 5.5 | 975 | 60 | 6.2 | 0.5604 | 1.11 ( 0.78, 1.59) | 1.12 ( 0.77, 1.64) | 0.01 (-0.01, 0.03) | |
| Female | 316 | 16 | 5.1 | 303 | 10 | 3.3 | 0.2744 | 0.65 ( 0.30, 1.41) | 0.64 ( 0.29, 1.43) | -0.02 (-0.05, 0.01) | |
| Age [years] | | | | | | | | | | | 0.5623 |
| <65 | 435 | 27 | 6.2 | 392 | 28 | 7.1 | 0.5896 | 1.15 ( 0.69, 1.92) | 1.16 ( 0.67, 2.01) | 0.01 (-0.02, 0.04) | |
| >=65 | 839 | 42 | 5.0 | 886 | 42 | 4.7 | 0.7979 | 0.95 ( 0.62, 1.44) | 0.94 ( 0.61, 1.46) | 0.00 (-0.02, 0.02) | |
| Region | | | | | | | | | | | 0.9424 |
| North America | 161 | 8 | 5.0 | 159 | 9 | 5.7 | 0.7828 | 1.14 ( 0.45, 2.88) | 1.15 ( 0.43, 3.05) | 0.01 (-0.04, 0.06) | |
| Latin America | 420 | 20 | 4.8 | 440 | 20 | 4.5 | 0.8802 | 0.95 ( 0.52, 1.75) | 0.95 ( 0.50, 1.80) | 0.00 (-0.03, 0.03) | |
| Europe | 469 | 20 | 4.3 | 467 | 17 | 3.6 | 0.6241 | 0.85 ( 0.45, 1.61) | 0.85 ( 0.44, 1.64) | -0.01 (-0.03, 0.02) | |
| Asia | 174 | 20 | 11.5 | 165 | 23 | 13.9 | 0.4989 | 1.21 ( 0.69, 2.12) | 1.25 ( 0.66, 2.37) | 0.02 (-0.05, 0.10) | |
| Other | 50 | 1 | 2.0 | 47 | 1 | 2.1 | 0.9647 | 1.06 ( 0.07, 16.53) | 1.07 ( 0.06, 17.53) | 0.00 (-0.06, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.9565 |
| Diabetic | 694 | 41 | 5.9 | 698 | 42 | 6.0 | 0.9313 | 1.02 ( 0.67, 1.55) | 1.02 ( 0.65, 1.59) | 0.00 (-0.02, 0.03) | |
| Non-Diabetic | 580 | 28 | 4.8 | 580 | 28 | 4.8 | 1.0000 | 1.00 ( 0.60, 1.67) | 1.00 ( 0.58, 1.71) | 0.00 (-0.02, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.2310 |
| <30 | 889 | 59 | 6.6 | 836 | 52 | 6.2 | 0.7245 | 0.94 ( 0.65, 1.34) | 0.93 ( 0.63, 1.37) | 0.00 (-0.03, 0.02) | |
| >=30 | 385 | 10 | 2.6 | 442 | 18 | 4.1 | 0.2421 | 1.57 ( 0.73, 3.36) | 1.59 ( 0.73, 3.49) | 0.01 (-0.01, 0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.7659 |
| <130 | 857 | 52 | 6.1 | 834 | 50 | 6.0 | 0.9501 | 0.99 ( 0.68, 1.44) | 0.99 ( 0.66, 1.47) | 0.00 (-0.02, 0.02) | |
| >=130 | 417 | 17 | 4.1 | 444 | 20 | 4.5 | 0.7571 | 1.10 ( 0.59, 2.08) | 1.11 ( 0.57, 2.15) | 0.00 (-0.02, 0.03) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.0880 |
| <75 | 718 | 38 | 5.3 | 678 | 45 | 6.6 | 0.2883 | 1.25 ( 0.82, 1.91) | 1.27 ( 0.82, 1.99) | 0.01 (-0.01, 0.04) | |
| 75 to <85 | 348 | 20 | 5.7 | 382 | 11 | 2.9 | 0.0550 | 0.50 ( 0.24, 1.03) | 0.49 ( 0.23, 1.03) | -0.03 (-0.06, 0.00) | |
| >=85 | 208 | 11 | 5.3 | 218 | 14 | 6.4 | 0.6188 | 1.21 ( 0.56, 2.61) | 1.23 ( 0.54, 2.77) | 0.01 (-0.03, 0.06) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
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Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3210 |
| <30 | 89 | 8 | 9.0 | 115 | 9 | 7.8 | 0.7657 | 0.87 ( 0.35, | 2.17) | 0.86 ( 0.32, | 2.33) | -0.01 (-0.09, | 0.07) | |
| 30 to <45 | 348 | 11 | 3.2 | 345 | 18 | 5.2 | 0.1764 | 1.65 ( 0.79, | 3.44) | 1.69 ( 0.78, | 3.63) | 0.02 (-0.01, | 0.05) | |
| >=45 | 837 | 50 | 6.0 | 818 | 43 | 5.3 | 0.5266 | 0.88 ( 0.59, | 1.31) | 0.87 ( 0.57, | 1.33) | -0.01 (-0.03, | 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4880 |
| Normal (<30) | 452 | 18 | 4.0 | 456 | 15 | 3.3 | 0.5770 | 0.83 ( 0.42, | 1.62) | 0.82 ( 0.41, | 1.65) | -0.01 (-0.03, | 0.02) | |
| Microalbuminuria (30 to <=300) | 627 | 39 | 6.2 | 608 | 36 | 5.9 | 0.8259 | 0.95 ( 0.61, | 1.48) | 0.95 ( 0.59, | 1.51) | 0.00 (-0.03, | 0.02) | |
| Macroalbuminuria (>300) | 189 | 12 | 6.3 | 207 | 19 | 9.2 | 0.2951 | 1.45 ( 0.72, | 2.90) | 1.49 ( 0.70, | 3.16) | 0.03 (-0.02, | 0.08) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1880 |
| Low, moderate or high | 953 | 50 | 5.2 | 947 | 43 | 4.5 | 0.4758 | 0.87 ( 0.58, | 1.29) | 0.86 ( 0.57, | 1.30) | -0.01 (-0.03, | 0.01) | |
| Very high | 315 | 19 | 6.0 | 325 | 27 | 8.3 | 0.2651 | 1.38 ( 0.78, | 2.43) | 1.41 ( 0.77, | 2.59) | 0.02 (-0.02, | 0.06) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4523 |
| No | 161 | 11 | 6.8 | 168 | 15 | 8.9 | 0.4811 | 1.31 ( 0.62, | 2.76) | 1.34 ( 0.59, | 3.01) | 0.02 (-0.04, | 0.08) | |
| Yes | 1113 | 58 | 5.2 | 1110 | 55 | 5.0 | 0.7834 | 0.95 ( 0.66, | 1.36) | 0.95 ( 0.65, | 1.38) | 0.00 (-0.02, | 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2713 |
| No | 62 | 5 | 8.1 | 72 | 10 | 13.9 | 0.2863 | 1.72 ( 0.62, | 4.77) | 1.84 ( 0.59, | 5.70) | 0.06 (-0.05, | 0.16) | |
| Yes | 1212 | 64 | 5.3 | 1206 | 60 | 5.0 | 0.7335 | 0.94 ( 0.67, | 1.33) | 0.94 ( 0.65, | 1.35) | 0.00 (-0.02, | 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1409 |
| No | 46 | 3 | 6.5 | 57 | 0 | 0 | 0.0797 | 0.12 (<0.01, | 2.19) | 0.11 (<0.01, | 2.15) | -0.07 (-0.14, | 0.01) | |
| Yes | 1228 | 66 | 5.4 | 1221 | 70 | 5.7 | 0.6986 | 1.07 ( 0.77, | 1.48) | 1.07 ( 0.76, | 1.51) | 0.00 (-0.01, | 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
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User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 1 | 0.1 | 1278 | 0 | 0 | 0.4780 | 0.33 ( 0.01, 8.15) | 0.33 ( 0.01, 8.16) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 958 | 1 | 0.1 | 975 | 0 | 0 | | | | | |
| Female | 316 | 0 | 0 | 303 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 1 | 0.2 | 392 | 0 | 0 | | | | | |
| >=65 | 839 | 0 | 0 | 886 | 0 | 0 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 0 | 0 | | | | | |
| Latin America | 420 | 0 | 0 | 440 | 0 | 0 | | | | | |
| Europe | 469 | 0 | 0 | 467 | 0 | 0 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 1 | 0.1 | 698 | 0 | 0 | | | | | |
| Non-Diabetic | 580 | 0 | 0 | 580 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 1 | 0.1 | 836 | 0 | 0 | | | | | |
| >=30 | 385 | 0 | 0 | 442 | 0 | 0 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 0 | 0 | 834 | 0 | 0 | | | | | |
| >=130 | 417 | 1 | 0.2 | 444 | 0 | 0 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 0 | 0 | 678 | 0 | 0 | | | | | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 0 | 0 | | | | | |
| >=85 | 208 | 0 | 0 | 218 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 0 | 0 | | | | | |
| 30 to <45 | 348 | 0 | 0 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 1 | 0.1 | 818 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 0 | 0 | 456 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 0 | 0 | 608 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 1 | 0.1 | 947 | 0 | 0 | | | | | |
| Very high | 315 | 0 | 0 | 325 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 0 | 0 | 168 | 0 | 0 | | | | | |
| Yes | 1113 | 1 | 0.1 | 1110 | 0 | 0 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 0 | 0 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 1 | 0.1 | 1206 | 0 | 0 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 0 | 0 | | | | | |
| Yes | 1228 | 1 | 0.1 | 1221 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 33 | 2.6 | 1278 | 32 | 2.5 | 0.8899 | 0.97 ( 0.60, 1.56) | 0.97 ( 0.59, 1.58) | 0.00 (-0.01, 0.01) | | |
| Sex | | | | | | | | | | | | 0.2759 |
| Male | 958 | 28 | 2.9 | 975 | 24 | 2.5 | 0.5309 | 0.84 ( 0.49, 1.44) | 0.84 ( 0.48, 1.46) | 0.00 (-0.02, 0.01) | | |
| Female | 316 | 5 | 1.6 | 303 | 8 | 2.6 | 0.3588 | 1.67 ( 0.55, 5.04) | 1.69 ( 0.55, 5.21) | 0.01 (-0.01, 0.03) | | |
| Age [years] | | | | | | | | | | | | 0.5438 |
| <65 | 435 | 15 | 3.4 | 392 | 11 | 2.8 | 0.5972 | 0.81 ( 0.38, 1.75) | 0.81 ( 0.37, 1.78) | -0.01 (-0.03, 0.02) | | |
| >=65 | 839 | 18 | 2.1 | 886 | 21 | 2.4 | 0.7536 | 1.10 ( 0.59, 2.06) | 1.11 ( 0.59, 2.09) | 0.00 (-0.01, 0.02) | | |
| Region | | | | | | | | | | | | 0.6206 |
| North America | 161 | 5 | 3.1 | 159 | 9 | 5.7 | 0.2639 | 1.82 ( 0.62, 5.32) | 1.87 ( 0.61, 5.71) | 0.03 (-0.02, 0.07) | | |
| Latin America | 420 | 11 | 2.6 | 440 | 11 | 2.5 | 0.9120 | 0.95 ( 0.42, 2.18) | 0.95 ( 0.41, 2.22) | 0.00 (-0.02, 0.02) | | |
| Europe | 469 | 8 | 1.7 | 467 | 7 | 1.5 | 0.8011 | 0.88 ( 0.32, 2.40) | 0.88 ( 0.32, 2.44) | 0.00 (-0.02, 0.01) | | |
| Asia | 174 | 7 | 4.0 | 165 | 3 | 1.8 | 0.2305 | 0.45 ( 0.12, 1.72) | 0.44 ( 0.11, 1.74) | -0.02 (-0.06, 0.01) | | |
| Other | 50 | 2 | 4.0 | 47 | 2 | 4.3 | 0.9496 | 1.06 ( 0.16, 7.25) | 1.07 ( 0.14, 7.90) | 0.00 (-0.08, 0.08) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2628 |
| Diabetic | 694 | 30 | 4.3 | 698 | 26 | 3.7 | 0.5703 | 0.86 ( 0.52, 1.44) | 0.86 ( 0.50, 1.46) | -0.01 (-0.03, 0.01) | | |
| Non-Diabetic | 580 | 3 | 0.5 | 580 | 6 | 1.0 | 0.3154 | 2.00 ( 0.50, 7.96) | 2.01 ( 0.50, 8.08) | 0.01 ( 0.00, 0.02) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9687 |
| <30 | 889 | 19 | 2.1 | 836 | 17 | 2.0 | 0.8803 | 0.95 ( 0.50, 1.82) | 0.95 ( 0.49, 1.84) | 0.00 (-0.01, 0.01) | | |
| >=30 | 385 | 14 | 3.6 | 442 | 15 | 3.4 | 0.8499 | 0.93 ( 0.46, 1.91) | 0.93 ( 0.44, 1.95) | 0.00 (-0.03, 0.02) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.6633 |
| <130 | 857 | 20 | 2.3 | 834 | 17 | 2.0 | 0.6781 | 0.87 ( 0.46, 1.66) | 0.87 ( 0.45, 1.67) | 0.00 (-0.02, 0.01) | | |
| >=130 | 417 | 13 | 3.1 | 444 | 15 | 3.4 | 0.8292 | 1.08 ( 0.52, 2.25) | 1.09 ( 0.51, 2.31) | 0.00 (-0.02, 0.03) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7406 |
| <75 | 718 | 16 | 2.2 | 678 | 15 | 2.2 | 0.9838 | 0.99 ( 0.49, 1.99) | 0.99 ( 0.49, 2.02) | 0.00 (-0.02, 0.02) | | |
| 75 to <85 | 348 | 10 | 2.9 | 382 | 8 | 2.1 | 0.4977 | 0.73 ( 0.29, 1.83) | 0.72 ( 0.28, 1.85) | -0.01 (-0.03, 0.01) | | |
| >=85 | 208 | 7 | 3.4 | 218 | 9 | 4.1 | 0.6788 | 1.23 ( 0.47, 3.23) | 1.24 ( 0.45, 3.38) | 0.01 (-0.03, 0.04) | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6643 |
| <30 | 89 | 3 | 3.4 | 115 | 6 | 5.2 | 0.5242 | 1.55 ( 0.40, 6.02) | 1.58 ( 0.38, 6.49) | 0.02 | (-0.04, 0.07) | |
| 30 to <45 | 348 | 11 | 3.2 | 345 | 8 | 2.3 | 0.4973 | 0.73 ( 0.30, 1.80) | 0.73 ( 0.29, 1.83) | -0.01 | (-0.03, 0.02) | |
| >=45 | 837 | 19 | 2.3 | 818 | 18 | 2.2 | 0.9238 | 0.97 ( 0.51, 1.83) | 0.97 ( 0.50, 1.86) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.6140 |
| Normal (<30) | 452 | 7 | 1.5 | 456 | 9 | 2.0 | 0.6265 | 1.27 ( 0.48, 3.39) | 1.28 ( 0.47, 3.47) | 0.00 | (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 627 | 14 | 2.2 | 608 | 14 | 2.3 | 0.9344 | 1.03 ( 0.50, 2.14) | 1.03 ( 0.49, 2.18) | 0.00 | (-0.02, 0.02) | |
| Macroalbuminuria (>300) | 189 | 12 | 6.3 | 207 | 9 | 4.3 | 0.3747 | 0.68 ( 0.30, 1.59) | 0.67 ( 0.28, 1.63) | -0.02 | (-0.06, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4189 |
| Low, moderate or high | 953 | 23 | 2.4 | 947 | 19 | 2.0 | 0.5462 | 0.83 ( 0.46, 1.52) | 0.83 ( 0.45, 1.53) | 0.00 | (-0.02, 0.01) | |
| Very high | 315 | 10 | 3.2 | 325 | 13 | 4.0 | 0.5749 | 1.26 ( 0.56, 2.83) | 1.27 ( 0.55, 2.94) | 0.01 | (-0.02, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5248 |
| No | 161 | 5 | 3.1 | 168 | 7 | 4.2 | 0.6078 | 1.34 ( 0.43, 4.14) | 1.36 ( 0.42, 4.36) | 0.01 | (-0.03, 0.05) | |
| Yes | 1113 | 28 | 2.5 | 1110 | 25 | 2.3 | 0.6839 | 0.90 ( 0.53, 1.53) | 0.89 ( 0.52, 1.54) | 0.00 | (-0.02, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3543 |
| No | 62 | 5 | 8.1 | 72 | 3 | 4.2 | 0.3424 | 0.52 ( 0.13, 2.08) | 0.50 ( 0.11, 2.16) | -0.04 | (-0.12, 0.04) | |
| Yes | 1212 | 28 | 2.3 | 1206 | 29 | 2.4 | 0.8784 | 1.04 ( 0.62, 1.74) | 1.04 ( 0.62, 1.76) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.6632 |
| No | 46 | 1 | 2.2 | 57 | 2 | 3.5 | 0.6888 | 1.61 ( 0.15, 17.25) | 1.64 ( 0.14, 18.64) | 0.01 | (-0.05, 0.08) | |
| Yes | 1228 | 32 | 2.6 | 1221 | 30 | 2.5 | 0.8146 | 0.94 ( 0.58, 1.54) | 0.94 ( 0.57, 1.56) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 78 | 6.1 | 1278 | 84 | 6.6 | 0.6409 | 1.07 ( 0.80, | 1.45) | 1.08 ( 0.78, | 1.48) | 0.00 (-0.01, 0.02) | |
| Sex | | | | | | | | | | | | | 0.1180 |
| Male | 958 | 47 | 4.9 | 975 | 42 | 4.3 | 0.5303 | 0.88 ( 0.58, | 1.32) | 0.87 ( 0.57, | 1.34) | -0.01 (-0.02, 0.01) | |
| Female | 316 | 31 | 9.8 | 303 | 42 | 13.9 | 0.1182 | 1.41 ( 0.91, | 2.19) | 1.48 ( 0.90, | 2.42) | 0.04 (-0.01, 0.09) | |
| Age [years] | | | | | | | | | | | | | 0.3657 |
| <65 | 435 | 27 | 6.2 | 392 | 21 | 5.4 | 0.6018 | 0.86 ( 0.50, | 1.50) | 0.86 ( 0.48, | 1.54) | -0.01 (-0.04, 0.02) | |
| >=65 | 839 | 51 | 6.1 | 886 | 63 | 7.1 | 0.3885 | 1.17 ( 0.82, | 1.67) | 1.18 ( 0.81, | 1.73) | 0.01 (-0.01, 0.03) | |
| Region | | | | | | | | | | | | | 0.3852 |
| North America | 161 | 17 | 10.6 | 159 | 13 | 8.2 | 0.4647 | 0.77 ( 0.39, | 1.54) | 0.75 ( 0.35, | 1.61) | -0.02 (-0.09, 0.04) | |
| Latin America | 420 | 24 | 5.7 | 440 | 22 | 5.0 | 0.6417 | 0.88 ( 0.50, | 1.54) | 0.87 ( 0.48, | 1.57) | -0.01 (-0.04, 0.02) | |
| Europe | 469 | 31 | 6.6 | 467 | 39 | 8.4 | 0.3112 | 1.26 ( 0.80, | 1.99) | 1.29 ( 0.79, | 2.10) | 0.02 (-0.02, 0.05) | |
| Asia | 174 | 3 | 1.7 | 165 | 8 | 4.8 | 0.1047 | 2.81 ( 0.76, | 10.42) | 2.90 ( 0.76, | 11.14) | 0.03 (-0.01, 0.07) | |
| Other | 50 | 3 | 6.0 | 47 | 2 | 4.3 | 0.6977 | 0.71 ( 0.12, | 4.06) | 0.70 ( 0.11, | 4.36) | -0.02 (-0.10, 0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.9072 |
| Diabetic | 694 | 47 | 6.8 | 698 | 50 | 7.2 | 0.7745 | 1.06 ( 0.72, | 1.55) | 1.06 ( 0.70, | 1.61) | 0.00 (-0.02, 0.03) | |
| Non-Diabetic | 580 | 31 | 5.3 | 580 | 34 | 5.9 | 0.7017 | 1.10 ( 0.68, | 1.76) | 1.10 ( 0.67, | 1.82) | 0.01 (-0.02, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.9194 |
| <30 | 889 | 48 | 5.4 | 836 | 47 | 5.6 | 0.8394 | 1.04 ( 0.70, | 1.54) | 1.04 ( 0.69, | 1.58) | 0.00 (-0.02, 0.02) | |
| >=30 | 385 | 30 | 7.8 | 442 | 37 | 8.4 | 0.7609 | 1.07 ( 0.68, | 1.70) | 1.08 ( 0.65, | 1.79) | 0.01 (-0.03, 0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.9088 |
| <130 | 857 | 52 | 6.1 | 834 | 55 | 6.6 | 0.6563 | 1.09 ( 0.75, | 1.57) | 1.09 ( 0.74, | 1.62) | 0.01 (-0.02, 0.03) | |
| >=130 | 417 | 26 | 6.2 | 444 | 29 | 6.5 | 0.8589 | 1.05 ( 0.63, | 1.75) | 1.05 ( 0.61, | 1.82) | 0.00 (-0.03, 0.04) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.3792 |
| <75 | 718 | 46 | 6.4 | 678 | 47 | 6.9 | 0.6939 | 1.08 ( 0.73, | 1.60) | 1.09 ( 0.71, | 1.66) | 0.01 (-0.02, 0.03) | |
| 75 to <85 | 348 | 21 | 6.0 | 382 | 30 | 7.9 | 0.3356 | 1.30 ( 0.76, | 2.23) | 1.33 ( 0.74, | 2.36) | 0.02 (-0.02, 0.05) | |
| >=85 | 208 | 11 | 5.3 | 218 | 7 | 3.2 | 0.2867 | 0.61 ( 0.24, | 1.54) | 0.59 ( 0.23, | 1.56) | -0.02 (-0.06, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.0088 |
| <30 | 89 | 4 | 4.5 | 115 | 15 | 13.0 | 0.0372 | 2.90 (<1.00, | 8.44) | 3.19 ( 1.02, | 9.97) | 0.09 ( 0.01, 0.16) | |
| 30 to <45 | 348 | 34 | 9.8 | 345 | 19 | 5.5 | 0.0348 | 0.56 ( 0.33, | 0.97) | 0.54 ( 0.30, | 0.96) | -0.04 (-0.08, 0.00) | |
| >=45 | 837 | 40 | 4.8 | 818 | 50 | 6.1 | 0.2317 | 1.28 ( 0.85, | 1.92) | 1.30 ( 0.85, | 1.99) | 0.01 (-0.01, 0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.2978 |
| Normal (<30) | 452 | 21 | 4.6 | 456 | 29 | 6.4 | 0.2577 | 1.37 ( 0.79, | 2.36) | 1.39 ( 0.78, | 2.48) | 0.02 (-0.01, 0.05) | |
| Microalbuminuria (30 to <=300) | 627 | 47 | 7.5 | 608 | 40 | 6.6 | 0.5289 | 0.88 ( 0.58, | 1.32) | 0.87 ( 0.56, | 1.35) | -0.01 (-0.04, 0.02) | |
| Macroalbuminuria (>300) | 189 | 9 | 4.8 | 207 | 15 | 7.2 | 0.3007 | 1.52 ( 0.68, | 3.40) | 1.56 ( 0.67, | 3.66) | 0.02 (-0.02, 0.07) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.5027 |
| Low, moderate or high | 953 | 52 | 5.5 | 947 | 60 | 6.3 | 0.4158 | 1.16 ( 0.81, | 1.66) | 1.17 ( 0.80, | 1.72) | 0.01 (-0.01, 0.03) | |
| Very high | 315 | 25 | 7.9 | 325 | 24 | 7.4 | 0.7929 | 0.93 ( 0.54, | 1.59) | 0.92 ( 0.52, | 1.66) | -0.01 (-0.05, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.1498 |
| No | 161 | 9 | 5.6 | 168 | 17 | 10.1 | 0.1280 | 1.81 ( 0.83, | 3.94) | 1.90 ( 0.82, | 4.40) | 0.05 (-0.01, 0.10) | |
| Yes | 1113 | 69 | 6.2 | 1110 | 67 | 6.0 | 0.8723 | 0.97 ( 0.70, | 1.35) | 0.97 ( 0.69, | 1.38) | 0.00 (-0.02, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.3043 |
| No | 62 | 8 | 12.9 | 72 | 6 | 8.3 | 0.3885 | 0.65 ( 0.24, | 1.76) | 0.61 ( 0.20, | 1.88) | -0.05 (-0.15, 0.06) | |
| Yes | 1212 | 70 | 5.8 | 1206 | 78 | 6.5 | 0.4778 | 1.12 ( 0.82, | 1.53) | 1.13 ( 0.81, | 1.57) | 0.01 (-0.01, 0.03) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.8930 |
| No | 46 | 2 | 4.3 | 57 | 3 | 5.3 | 0.8299 | 1.21 ( 0.21, | 6.94) | 1.22 ( 0.20, | 7.64) | 0.01 (-0.07, 0.09) | |
| Yes | 1228 | 76 | 6.2 | 1221 | 81 | 6.6 | 0.6531 | 1.07 ( 0.79, | 1.45) | 1.08 ( 0.78, | 1.49) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 8 | 0.6 | 1278 | 20 | 1.6 | 0.0231 | 2.49 ( 1.10, | 5.64) | 2.52 ( 1.10, | 5.73) | 0.01 ( 0.00, 0.02) | |
| Sex | | | | | | | | | | | | | 0.5028 |
| Male | 958 | 5 | 0.5 | 975 | 10 | 1.0 | 0.2070 | 1.97 ( 0.67, | 5.73) | 1.98 ( 0.67, | 5.80) | 0.01 ( 0.00, 0.01) | |
| Female | 316 | 3 | 0.9 | 303 | 10 | 3.3 | 0.0414 | 3.48 ( 0.97, | 12.51) | 3.56 ( 0.97, | 13.07) | 0.02 ( 0.00, 0.05) | |
| Age [years] | | | | | | | | | | | | | 0.3766 |
| <65 | 435 | 5 | 1.1 | 392 | 8 | 2.0 | 0.3035 | 1.78 ( 0.59, | 5.38) | 1.79 ( 0.58, | 5.52) | 0.01 (-0.01, 0.03) | |
| >=65 | 839 | 3 | 0.4 | 886 | 12 | 1.4 | 0.0258 | 3.79 ( 1.07, | 13.38) | 3.83 ( 1.08, | 13.61) | 0.01 ( 0.00, 0.02) | |
| Region | | | | | | | | | | | | | 0.9623 |
| North America | 161 | 2 | 1.2 | 159 | 5 | 3.1 | 0.2447 | 2.53 ( 0.50, | 12.86) | 2.58 ( 0.49, | 13.50) | 0.02 (-0.01, 0.05) | |
| Latin America | 420 | 2 | 0.5 | 440 | 7 | 1.6 | 0.1083 | 3.34 ( 0.70, | 15.99) | 3.38 ( 0.70, | 16.36) | 0.01 ( 0.00, 0.02) | |
| Europe | 469 | 4 | 0.9 | 467 | 7 | 1.5 | 0.3591 | 1.76 ( 0.52, | 5.96) | 1.77 ( 0.51, | 6.08) | 0.01 (-0.01, 0.02) | |
| Asia | 174 | 0 | 0 | 165 | 1 | 0.6 | 0.4551 | 3.16 ( 0.13, | 77.09) | 3.18 ( 0.13, | 78.67) | 0.01 (-0.01, 0.02) | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 ( 0.02, | 52.49) | 1.06 ( 0.02, | 54.66) | 0.00 (-0.04, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.4678 |
| Diabetic | 694 | 4 | 0.6 | 698 | 13 | 1.9 | 0.0289 | 3.23 ( 1.06, | 9.86) | 3.27 ( 1.06, | 10.09) | 0.01 ( 0.00, 0.02) | |
| Non-Diabetic | 580 | 4 | 0.7 | 580 | 7 | 1.2 | 0.3634 | 1.75 ( 0.52, | 5.95) | 1.76 ( 0.51, | 6.04) | 0.01 (-0.01, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.4518 |
| <30 | 889 | 6 | 0.7 | 836 | 11 | 1.3 | 0.1781 | 1.95 ( 0.72, | 5.25) | 1.96 ( 0.72, | 5.33) | 0.01 ( 0.00, 0.02) | |
| >=30 | 385 | 2 | 0.5 | 442 | 9 | 2.0 | 0.0575 | 3.92 ( 0.85, | 18.03) | 3.98 ( 0.85, | 18.54) | 0.02 ( 0.00, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.8186 |
| <130 | 857 | 5 | 0.6 | 834 | 13 | 1.6 | 0.0507 | 2.67 ( 0.96, | 7.46) | 2.70 ( 0.96, | 7.60) | 0.01 ( 0.00, 0.02) | |
| >=130 | 417 | 3 | 0.7 | 444 | 7 | 1.6 | 0.2407 | 2.19 ( 0.57, | 8.42) | 2.21 ( 0.57, | 8.61) | 0.01 (-0.01, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.3806 |
| <75 | 718 | 6 | 0.8 | 678 | 9 | 1.3 | 0.3731 | 1.59 ( 0.57, | 4.44) | 1.60 ( 0.57, | 4.51) | 0.00 (-0.01, 0.02) | |
| 75 to <85 | 348 | 0 | 0 | 382 | 7 | 1.8 | 0.0183 | 13.67 ( 0.78, | 238.44) | 13.92 ( 0.79, | 244.66) | 0.02 ( 0.00, 0.03) | |
| >=85 | 208 | 2 | 1.0 | 218 | 4 | 1.8 | 0.4445 | 1.91 ( 0.35, | 10.31) | 1.93 ( 0.35, | 10.62) | 0.01 (-0.01, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3810 |
| <30 | 89 | 0 | 0 | 115 | 1 | 0.9 | 0.5923 | 2.33 ( 0.10, 56.46) | 2.34 ( 0.09, 58.25) | 0.01 (-0.02, 0.03) | |
| 30 to <45 | 348 | 1 | 0.3 | 345 | 8 | 2.3 | 0.0182 | 8.07 ( 1.01, 64.18) | 8.24 ( 1.02, 66.22) | 0.02 ( 0.00, 0.04) | |
| >=45 | 837 | 7 | 0.8 | 818 | 11 | 1.3 | 0.3188 | 1.61 ( 0.63, 4.13) | 1.62 ( 0.62, 4.19) | 0.01 ( 0.00, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.5056 |
| Normal (<30) | 452 | 2 | 0.4 | 456 | 8 | 1.8 | 0.0582 | 3.96 ( 0.85, 18.57) | 4.02 ( 0.85, 19.02) | 0.01 ( 0.00, 0.03) | |
| Microalbuminuria (30 to <=300) | 627 | 4 | 0.6 | 608 | 10 | 1.6 | 0.0948 | 2.58 ( 0.81, 8.18) | 2.60 ( 0.81, 8.35) | 0.01 ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 207 | 2 | 1.0 | 0.9271 | 0.91 ( 0.13, 6.42) | 0.91 ( 0.13, 6.54) | 0.00 (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.2679 |
| Low, moderate or high | 953 | 7 | 0.7 | 947 | 13 | 1.4 | 0.1729 | 1.87 ( 0.75, 4.66) | 1.88 ( 0.75, 4.74) | 0.01 ( 0.00, 0.02) | |
| Very high | 315 | 1 | 0.3 | 325 | 7 | 2.2 | 0.0366 | 6.78 ( 0.84, 54.83) | 6.91 ( 0.85, 56.51) | 0.02 ( 0.00, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.9107 |
| No | 161 | 0 | 0 | 168 | 1 | 0.6 | 0.4969 | 2.88 ( 0.12, 70.08) | 2.89 ( 0.12, 71.52) | 0.01 (-0.01, 0.02) | |
| Yes | 1113 | 8 | 0.7 | 1110 | 19 | 1.7 | 0.0326 | 2.38 ( 1.05, 5.42) | 2.41 ( 1.05, 5.52) | 0.01 ( 0.00, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.1713 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 ( 0.01, 6.94) | 0.28 ( 0.01, 7.07) | -0.02 (-0.06, 0.03) | |
| Yes | 1212 | 7 | 0.6 | 1206 | 20 | 1.7 | 0.0114 | 2.87 ( 1.22, 6.77) | 2.90 ( 1.22, 6.89) | 0.01 ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.4064 |
| No | 46 | 1 | 2.2 | 57 | 1 | 1.8 | 0.8781 | 0.81 ( 0.05, 12.55) | 0.80 ( 0.05, 13.21) | 0.00 (-0.06, 0.05) | |
| Yes | 1228 | 7 | 0.6 | 1221 | 19 | 1.6 | 0.0173 | 2.73 ( 1.15, 6.47) | 2.76 ( 1.15, 6.58) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 6 | 0.5 | 1278 | 6 | 0.5 | 0.9957 | 1.00 ( 0.32, 3.08) | 1.00 ( 0.32, 3.10) | 0.00 (-0.01, 0.01) | |
| Sex | | | | | | | | | | | |
| Male | 958 | 5 | 0.5 | 975 | 1 | 0.1 | | | | | |
| Female | 316 | 1 | 0.3 | 303 | 5 | 1.7 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 2 | 0.5 | 392 | 1 | 0.3 | | | | | |
| >=65 | 839 | 4 | 0.5 | 886 | 5 | 0.6 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 1 | 0.6 | | | | | |
| Latin America | 420 | 2 | 0.5 | 440 | 2 | 0.5 | | | | | |
| Europe | 469 | 2 | 0.4 | 467 | 3 | 0.6 | | | | | |
| Asia | 174 | 1 | 0.6 | 165 | 0 | 0 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 5 | 0.7 | 698 | 2 | 0.3 | | | | | |
| Non-Diabetic | 580 | 1 | 0.2 | 580 | 4 | 0.7 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 3 | 0.3 | 836 | 4 | 0.5 | | | | | |
| >=30 | 385 | 3 | 0.8 | 442 | 2 | 0.5 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 3 | 0.4 | 834 | 3 | 0.4 | | | | | |
| >=130 | 417 | 3 | 0.7 | 444 | 3 | 0.7 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 5 | 0.7 | 678 | 4 | 0.6 | | | | | |
| 75 to <85 | 348 | 0 | 0 | 382 | 2 | 0.5 | | | | | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 2 | 1.7 | | | | | |
| 30 to <45 | 348 | 3 | 0.9 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 3 | 0.4 | 818 | 4 | 0.5 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 1 | 0.2 | 456 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 3 | 0.5 | 608 | 5 | 0.8 | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 2 | 0.2 | 947 | 4 | 0.4 | | | | | |
| Very high | 315 | 3 | 1.0 | 325 | 2 | 0.6 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.4769 |
| No | 161 | 0 | 0 | 168 | 1 | 0.6 | 0.4969 | 2.88 ( 0.12, 70.08) | 2.89 ( 0.12, 71.52) | 0.01 (-0.01, 0.02) | |
| Yes | 1113 | 6 | 0.5 | 1110 | 5 | 0.5 | 0.7659 | 0.84 ( 0.26, 2.73) | 0.83 ( 0.25, 2.74) | 0.00 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.4081 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 ( 0.01, 6.94) | 0.28 ( 0.01, 7.07) | -0.02 (-0.06, 0.03) | |
| Yes | 1212 | 5 | 0.4 | 1206 | 6 | 0.5 | 0.7562 | 1.21 ( 0.37, 3.94) | 1.21 ( 0.37, 3.97) | 0.00 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.3869 |
| No | 46 | 1 | 2.2 | 57 | 0 | 0 | 0.3852 | 0.27 ( 0.01, 6.48) | 0.26 ( 0.01, 6.63) | -0.02 (-0.08, 0.03) | |
| Yes | 1228 | 5 | 0.4 | 1221 | 6 | 0.5 | 0.7553 | 1.21 ( 0.37, 3.94) | 1.21 ( 0.37, 3.97) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 38 | 3.0 | 1278 | 38 | 3.0 | 0.9889 | 1.00 ( 0.64, 1.55) | 1.00 ( 0.63, 1.57) | 0.00 (-0.01, 0.01) | |
| Sex | | | | | | | | | | | 0.2389 |
| Male | 958 | 25 | 2.6 | 975 | 30 | 3.1 | 0.5367 | 1.18 ( 0.70, 1.99) | 1.18 ( 0.69, 2.03) | 0.00 (-0.01, 0.02) | |
| Female | 316 | 13 | 4.1 | 303 | 8 | 2.6 | 0.3114 | 0.64 ( 0.27, 1.53) | 0.63 ( 0.26, 1.55) | -0.01 (-0.04, 0.01) | |
| Age [years] | | | | | | | | | | | 0.1728 |
| <65 | 435 | 8 | 1.8 | 392 | 3 | 0.8 | 0.1783 | 0.42 ( 0.11, 1.56) | 0.41 ( 0.11, 1.56) | -0.01 (-0.03, 0.00) | |
| >=65 | 839 | 30 | 3.6 | 886 | 35 | 4.0 | 0.6830 | 1.10 ( 0.68, 1.78) | 1.11 ( 0.67, 1.82) | 0.00 (-0.01, 0.02) | |
| Region | | | | | | | | | | | 0.4219 |
| North America | 161 | 5 | 3.1 | 159 | 7 | 4.4 | 0.5415 | 1.42 ( 0.46, 4.37) | 1.44 ( 0.45, 4.63) | 0.01 (-0.03, 0.05) | |
| Latin America | 420 | 9 | 2.1 | 440 | 5 | 1.1 | 0.2437 | 0.53 ( 0.18, 1.57) | 0.52 ( 0.17, 1.58) | -0.01 (-0.03, 0.01) | |
| Europe | 469 | 18 | 3.8 | 467 | 15 | 3.2 | 0.6036 | 0.84 ( 0.43, 1.64) | 0.83 ( 0.41, 1.67) | -0.01 (-0.03, 0.02) | |
| Asia | 174 | 5 | 2.9 | 165 | 10 | 6.1 | 0.1538 | 2.11 ( 0.74, 6.04) | 2.18 ( 0.73, 6.52) | 0.03 (-0.01, 0.08) | |
| Other | 50 | 1 | 2.0 | 47 | 1 | 2.1 | 0.9647 | 1.06 ( 0.07, 16.53) | 1.07 ( 0.06, 17.53) | 0.00 (-0.06, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.0111 |
| Diabetic | 694 | 26 | 3.7 | 698 | 15 | 2.1 | 0.0780 | 0.57 ( 0.31, 1.07) | 0.56 ( 0.30, 1.07) | -0.02 (-0.03, 0.00) | |
| Non-Diabetic | 580 | 12 | 2.1 | 580 | 23 | 4.0 | 0.0590 | 1.92 ( 0.96, 3.82) | 1.95 ( 0.96, 3.97) | 0.02 ( 0.00, 0.04) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.7333 |
| <30 | 889 | 31 | 3.5 | 836 | 31 | 3.7 | 0.8053 | 1.06 ( 0.65, 1.73) | 1.07 ( 0.64, 1.77) | 0.00 (-0.02, 0.02) | |
| >=30 | 385 | 7 | 1.8 | 442 | 7 | 1.6 | 0.7943 | 0.87 ( 0.31, 2.46) | 0.87 ( 0.30, 2.50) | 0.00 (-0.02, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.8456 |
| <130 | 857 | 23 | 2.7 | 834 | 23 | 2.8 | 0.9255 | 1.03 ( 0.58, 1.82) | 1.03 ( 0.57, 1.85) | 0.00 (-0.01, 0.02) | |
| >=130 | 417 | 15 | 3.6 | 444 | 15 | 3.4 | 0.8611 | 0.94 ( 0.46, 1.90) | 0.94 ( 0.45, 1.94) | 0.00 (-0.03, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.5239 |
| <75 | 718 | 26 | 3.6 | 678 | 24 | 3.5 | 0.9349 | 0.98 ( 0.57, 1.69) | 0.98 ( 0.56, 1.72) | 0.00 (-0.02, 0.02) | |
| 75 to <85 | 348 | 10 | 2.9 | 382 | 9 | 2.4 | 0.6609 | 0.82 ( 0.34, 1.99) | 0.82 ( 0.33, 2.03) | -0.01 (-0.03, 0.02) | |
| >=85 | 208 | 2 | 1.0 | 218 | 5 | 2.3 | 0.2797 | 2.39 ( 0.47, 12.16) | 2.42 ( 0.46, 12.60) | 0.01 (-0.01, 0.04) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.2889 |
| <30 | 89 | 4 | 4.5 | 115 | 3 | 2.6 | 0.4631 | 0.58 ( 0.13, 2.53) | 0.57 ( 0.12, 2.61) | -0.02 (-0.07, 0.03) | |
| 30 to <45 | 348 | 15 | 4.3 | 345 | 10 | 2.9 | 0.3190 | 0.67 ( 0.31, 1.48) | 0.66 ( 0.29, 1.50) | -0.01 (-0.04, 0.01) | |
| >=45 | 837 | 19 | 2.3 | 818 | 25 | 3.1 | 0.3202 | 1.35 ( 0.75, 2.43) | 1.36 ( 0.74, 2.48) | 0.01 (-0.01, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.2507 |
| Normal (<30) | 452 | 17 | 3.8 | 456 | 11 | 2.4 | 0.2398 | 0.64 ( 0.30, 1.35) | 0.63 ( 0.29, 1.37) | -0.01 (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 15 | 2.4 | 608 | 21 | 3.5 | 0.2676 | 1.44 ( 0.75, 2.77) | 1.46 ( 0.75, 2.86) | 0.01 (-0.01, 0.03) | |
| Macroalbuminuria (>300) | 189 | 6 | 3.2 | 207 | 5 | 2.4 | 0.6461 | 0.76 ( 0.24, 2.45) | 0.75 ( 0.23, 2.52) | -0.01 (-0.04, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.7377 |
| Low, moderate or high | 953 | 27 | 2.8 | 947 | 28 | 3.0 | 0.8724 | 1.04 ( 0.62, 1.76) | 1.04 ( 0.61, 1.79) | 0.00 (-0.01, 0.02) | |
| Very high | 315 | 11 | 3.5 | 325 | 10 | 3.1 | 0.7682 | 0.88 ( 0.38, 2.05) | 0.88 ( 0.37, 2.10) | 0.00 (-0.03, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.1346 |
| No | 161 | 7 | 4.3 | 168 | 13 | 7.7 | 0.1983 | 1.78 ( 0.73, 4.35) | 1.85 ( 0.72, 4.75) | 0.03 (-0.02, 0.09) | |
| Yes | 1113 | 31 | 2.8 | 1110 | 25 | 2.3 | 0.4226 | 0.81 ( 0.48, 1.36) | 0.80 ( 0.47, 1.37) | -0.01 (-0.02, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.8315 |
| No | 62 | 4 | 6.5 | 72 | 4 | 5.6 | 0.8272 | 0.86 ( 0.22, 3.30) | 0.85 ( 0.20, 3.56) | -0.01 (-0.09, 0.07) | |
| Yes | 1212 | 34 | 2.8 | 1206 | 34 | 2.8 | 0.9834 | 1.00 ( 0.63, 1.61) | 1.01 ( 0.62, 1.63) | 0.00 (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.4126 |
| No | 46 | 1 | 2.2 | 57 | 0 | 0 | 0.3852 | 0.27 ( 0.01, 6.48) | 0.26 ( 0.01, 6.63) | -0.02 (-0.08, 0.03) | |
| Yes | 1228 | 37 | 3.0 | 1221 | 38 | 3.1 | 0.8867 | 1.03 ( 0.66, 1.61) | 1.03 ( 0.65, 1.64) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 6 | 0.5 | 1278 | 9 | 0.7 | 0.4408 | 1.50 ( 0.53, 4.19) | 1.50 ( 0.53, 4.22) | 0.00 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | 0.3315 |
| Male | 958 | 4 | 0.4 | 975 | 8 | 0.8 | 0.2594 | 1.97 ( 0.59, 6.50) | 1.97 ( 0.59, 6.57) | 0.00 ( 0.00, 0.01) | |
| Female | 316 | 2 | 0.6 | 303 | 1 | 0.3 | 0.5875 | 0.52 ( 0.05, 5.72) | 0.52 ( 0.05, 5.76) | 0.00 (-0.01, 0.01) | |
| Age [years] | | | | | | | | | | | 0.7333 |
| <65 | 435 | 2 | 0.5 | 392 | 2 | 0.5 | 0.9169 | 1.11 ( 0.16, 7.84) | 1.11 ( 0.16, 7.92) | 0.00 (-0.01, 0.01) | |
| >=65 | 839 | 4 | 0.5 | 886 | 7 | 0.8 | 0.4139 | 1.66 ( 0.49, 5.64) | 1.66 ( 0.48, 5.70) | 0.00 ( 0.00, 0.01) | |
| Region | | | | | | | | | | | |
| North America | 161 | 2 | 1.2 | 159 | 2 | 1.3 | | | | | |
| Latin America | 420 | 0 | 0 | 440 | 1 | 0.2 | | | | | |
| Europe | 469 | 4 | 0.9 | 467 | 5 | 1.1 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 1 | 0.6 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | 0.6381 |
| Diabetic | 694 | 4 | 0.6 | 698 | 7 | 1.0 | 0.3689 | 1.74 ( 0.51, 5.92) | 1.75 ( 0.51, 6.00) | 0.00 (-0.01, 0.01) | |
| Non-Diabetic | 580 | 2 | 0.3 | 580 | 2 | 0.3 | 1.0000 | 1.00 ( 0.14, 7.08) | 1.00 ( 0.14, 7.12) | 0.00 (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.6601 |
| <30 | 889 | 5 | 0.6 | 836 | 8 | 1.0 | 0.3437 | 1.70 ( 0.56, 5.18) | 1.71 ( 0.56, 5.24) | 0.00 ( 0.00, 0.01) | |
| >=30 | 385 | 1 | 0.3 | 442 | 1 | 0.2 | 0.9221 | 0.87 ( 0.05, 13.88) | 0.87 ( 0.05, 13.97) | 0.00 (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 5 | 0.6 | 834 | 4 | 0.5 | | | | | |
| >=130 | 417 | 1 | 0.2 | 444 | 5 | 1.1 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.3171 |
| <75 | 718 | 3 | 0.4 | 678 | 7 | 1.0 | 0.1735 | 2.47 ( 0.64, 9.52) | 2.49 ( 0.64, 9.65) | 0.01 ( 0.00, 0.02) | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 2 | 0.5 | 0.6183 | 1.82 ( 0.17, 20.01) | 1.83 ( 0.16, 20.23) | 0.00 (-0.01, 0.01) | |
| >=85 | 208 | 2 | 1.0 | 218 | 0 | 0 | 0.2303 | 0.19 (<0.01, 3.95) | 0.19 (<0.01, 3.96) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.5036 |
| <30 | 89 | 1 | 1.1 | 115 | 0 | 0 | 0.3697 | 0.26 ( 0.01, 6.27) | 0.26 ( 0.01, 6.35) | -0.01 (-0.04, 0.02) | |
| 30 to <45 | 348 | 0 | 0 | 345 | 1 | 0.3 | 0.4751 | 3.03 ( 0.12, 74.02) | 3.03 ( 0.12, 74.76) | 0.00 (-0.01, 0.01) | |
| >=45 | 837 | 5 | 0.6 | 818 | 8 | 1.0 | 0.3805 | 1.64 ( 0.54, 4.98) | 1.64 ( 0.54, 5.04) | 0.00 ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 0 | 0 | 456 | 3 | 0.7 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 4 | 0.6 | 608 | 4 | 0.7 | | | | | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 207 | 2 | 1.0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8137 |
| Low, moderate or high | 953 | 5 | 0.5 | 947 | 7 | 0.7 | 0.5551 | 1.41 ( 0.45, 4.42) | 1.41 ( 0.45, 4.46) | 0.00 ( 0.00, 0.01) | |
| Very high | 315 | 1 | 0.3 | 325 | 2 | 0.6 | 0.5812 | 1.94 ( 0.18, 21.27) | 1.94 ( 0.18, 21.55) | 0.00 (-0.01, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3904 |
| No | 161 | 0 | 0 | 168 | 2 | 1.2 | 0.2613 | 4.79 ( 0.23, 99.07) | 4.85 ( 0.23,101.80) | 0.01 (-0.01, 0.03) | |
| Yes | 1113 | 6 | 0.5 | 1110 | 7 | 0.6 | 0.7771 | 1.17 ( 0.39, 3.47) | 1.17 ( 0.39, 3.50) | 0.00 (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6801 |
| No | 62 | 1 | 1.6 | 72 | 1 | 1.4 | 0.9151 | 0.86 ( 0.05, 13.48) | 0.86 ( 0.05, 14.03) | 0.00 (-0.04, 0.04) | |
| Yes | 1212 | 5 | 0.4 | 1206 | 8 | 0.7 | 0.3991 | 1.61 ( 0.53, 4.90) | 1.61 ( 0.53, 4.94) | 0.00 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.7276 |
| No | 46 | 0 | 0 | 57 | 1 | 1.8 | 0.5704 | 2.43 ( 0.10, 58.31) | 2.47 ( 0.10, 62.05) | 0.02 (-0.04, 0.07) | |
| Yes | 1228 | 6 | 0.5 | 1221 | 8 | 0.7 | 0.5845 | 1.34 ( 0.47, 3.85) | 1.34 ( 0.46, 3.88) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 162 | 12.7 | 1278 | 155 | 12.1 | 0.6528 | 0.95 | ( 0.78, 1.17) | 0.95 | ( 0.75, 1.20) | -0.01 | (-0.03, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.7271 |
| Male | 958 | 122 | 12.7 | 975 | 116 | 11.9 | 0.5753 | 0.93 | ( 0.74, 1.19) | 0.93 | ( 0.71, 1.21) | -0.01 | (-0.04, 0.02) | |
| Female | 316 | 40 | 12.7 | 303 | 39 | 12.9 | 0.9367 | 1.02 | ( 0.67, 1.54) | 1.02 | ( 0.64, 1.63) | 0.00 | (-0.05, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.3908 |
| <65 | 435 | 55 | 12.6 | 392 | 41 | 10.5 | 0.3275 | 0.83 | ( 0.57, 1.21) | 0.81 | ( 0.53, 1.24) | -0.02 | (-0.07, 0.02) | |
| >=65 | 839 | 107 | 12.8 | 886 | 114 | 12.9 | 0.9438 | 1.01 | ( 0.79, 1.29) | 1.01 | ( 0.76, 1.34) | 0.00 | (-0.03, 0.03) | |
| Region | | | | | | | | | | | | | | 0.8755 |
| North America | 161 | 40 | 24.8 | 159 | 37 | 23.3 | 0.7419 | 0.94 | ( 0.63, 1.38) | 0.92 | ( 0.55, 1.53) | -0.02 | (-0.11, 0.08) | |
| Latin America | 420 | 49 | 11.7 | 440 | 43 | 9.8 | 0.3691 | 0.84 | ( 0.57, 1.23) | 0.82 | ( 0.53, 1.26) | -0.02 | (-0.06, 0.02) | |
| Europe | 469 | 50 | 10.7 | 467 | 49 | 10.5 | 0.9332 | 0.98 | ( 0.68, 1.43) | 0.98 | ( 0.65, 1.49) | 0.00 | (-0.04, 0.04) | |
| Asia | 174 | 20 | 11.5 | 165 | 22 | 13.3 | 0.6075 | 1.16 | ( 0.66, 2.04) | 1.18 | ( 0.62, 2.26) | 0.02 | (-0.05, 0.09) | |
| Other | 50 | 3 | 6.0 | 47 | 4 | 8.5 | 0.6330 | 1.42 | ( 0.34, 6.00) | 1.46 | ( 0.31, 6.89) | 0.03 | (-0.08, 0.13) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0791 |
| Diabetic | 694 | 81 | 11.7 | 698 | 92 | 13.2 | 0.3935 | 1.13 | ( 0.85, 1.49) | 1.15 | ( 0.84, 1.58) | 0.02 | (-0.02, 0.05) | |
| Non-Diabetic | 580 | 81 | 14.0 | 580 | 63 | 10.9 | 0.1090 | 0.78 | ( 0.57, 1.06) | 0.75 | ( 0.53, 1.07) | -0.03 | (-0.07, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0797 |
| <30 | 889 | 107 | 12.0 | 836 | 109 | 13.0 | 0.5296 | 1.08 | ( 0.84, 1.39) | 1.10 | ( 0.82, 1.46) | 0.01 | (-0.02, 0.04) | |
| >=30 | 385 | 55 | 14.3 | 442 | 46 | 10.4 | 0.0893 | 0.73 | ( 0.50, 1.05) | 0.70 | ( 0.46, 1.06) | -0.04 | (-0.08, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2059 |
| <130 | 857 | 123 | 14.4 | 834 | 124 | 14.9 | 0.7640 | 1.04 | ( 0.82, 1.30) | 1.04 | ( 0.80, 1.37) | 0.01 | (-0.03, 0.04) | |
| >=130 | 417 | 39 | 9.4 | 444 | 31 | 7.0 | 0.2034 | 0.75 | ( 0.47, 1.17) | 0.73 | ( 0.44, 1.19) | -0.02 | (-0.06, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7611 |
| <75 | 718 | 109 | 15.2 | 678 | 99 | 14.6 | 0.7613 | 0.96 | ( 0.75, 1.24) | 0.96 | ( 0.71, 1.28) | -0.01 | (-0.04, 0.03) | |
| 75 to <85 | 348 | 35 | 10.1 | 382 | 41 | 10.7 | 0.7653 | 1.07 | ( 0.70, 1.64) | 1.08 | ( 0.67, 1.73) | 0.01 | (-0.04, 0.05) | |
| >=85 | 208 | 18 | 8.7 | 218 | 15 | 6.9 | 0.4938 | 0.80 | ( 0.41, 1.54) | 0.78 | ( 0.38, 1.59) | -0.02 | (-0.07, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1250 |
| <30 | 89 | 17 | 19.1 | 115 | 20 | 17.4 | 0.7533 | 0.91 ( 0.51, 1.63) | 0.89 ( 0.44, 1.82) | -0.02 | (-0.12, 0.09) | |
| 30 to <45 | 348 | 56 | 16.1 | 345 | 38 | 11.0 | 0.0510 | 0.68 ( 0.47, >1.00) | 0.65 ( 0.41, 1.00) | -0.05 | (-0.10, 0.00) | |
| >=45 | 837 | 89 | 10.6 | 818 | 97 | 11.9 | 0.4302 | 1.12 ( 0.85, 1.46) | 1.13 ( 0.83, 1.53) | 0.01 | (-0.02, 0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.3820 |
| Normal (<30) | 452 | 56 | 12.4 | 456 | 58 | 12.7 | 0.8808 | 1.03 ( 0.73, 1.45) | 1.03 ( 0.70, 1.53) | 0.00 | (-0.04, 0.05) | |
| Microalbuminuria (30 to <=300) | 627 | 81 | 12.9 | 608 | 79 | 13.0 | 0.9688 | 1.01 ( 0.75, 1.34) | 1.01 ( 0.72, 1.40) | 0.00 | (-0.04, 0.04) | |
| Macroalbuminuria (>300) | 189 | 25 | 13.2 | 207 | 18 | 8.7 | 0.1477 | 0.66 ( 0.37, 1.17) | 0.62 ( 0.33, 1.19) | -0.05 | (-0.11, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0471 |
| Low, moderate or high | 953 | 106 | 11.1 | 947 | 115 | 12.1 | 0.4877 | 1.09 ( 0.85, 1.40) | 1.10 ( 0.83, 1.46) | 0.01 | (-0.02, 0.04) | |
| Very high | 315 | 56 | 17.8 | 325 | 40 | 12.3 | 0.0527 | 0.69 ( 0.48, 1.01) | 0.65 ( 0.42, 1.01) | -0.05 | (-0.11, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.8470 |
| No | 161 | 23 | 14.3 | 168 | 24 | 14.3 | 1.0000 | 1.00 ( 0.59, 1.70) | 1.00 ( 0.54, 1.85) | 0.00 | (-0.08, 0.08) | |
| Yes | 1113 | 139 | 12.5 | 1110 | 131 | 11.8 | 0.6201 | 0.94 ( 0.76, 1.18) | 0.94 ( 0.73, 1.21) | -0.01 | (-0.03, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6187 |
| No | 62 | 9 | 14.5 | 72 | 8 | 11.1 | 0.5549 | 0.77 ( 0.31, 1.86) | 0.74 ( 0.27, 2.04) | -0.03 | (-0.15, 0.08) | |
| Yes | 1212 | 153 | 12.6 | 1206 | 147 | 12.2 | 0.7458 | 0.97 ( 0.78, 1.19) | 0.96 ( 0.75, 1.22) | 0.00 | (-0.03, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.5337 |
| No | 46 | 5 | 10.9 | 57 | 4 | 7.0 | 0.4913 | 0.65 ( 0.18, 2.27) | 0.62 ( 0.16, 2.45) | -0.04 | (-0.15, 0.07) | |
| Yes | 1228 | 157 | 12.8 | 1221 | 151 | 12.4 | 0.7550 | 0.97 ( 0.78, 1.19) | 0.96 ( 0.76, 1.22) | 0.00 | (-0.03, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 144 | 11.3 | 1278 | 138 | 10.8 | 0.6842 | 0.96 ( 0.77, | 1.19) | 0.95 ( 0.74, | 1.22) | -0.01 (-0.03, | 0.02) | |
| Sex | | | | | | | | | | | | | | 0.8771 |
| Male | 958 | 108 | 11.3 | 975 | 104 | 10.7 | 0.6695 | 0.95 ( 0.73, | 1.22) | 0.94 ( 0.71, | 1.25) | -0.01 (-0.03, | 0.02) | |
| Female | 316 | 36 | 11.4 | 303 | 34 | 11.2 | 0.9464 | 0.98 ( 0.63, | 1.53) | 0.98 ( 0.60, | 1.62) | 0.00 (-0.05, | 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.7561 |
| <65 | 435 | 49 | 11.3 | 392 | 40 | 10.2 | 0.6232 | 0.91 ( 0.61, | 1.34) | 0.90 ( 0.58, | 1.39) | -0.01 (-0.05, | 0.03) | |
| >=65 | 839 | 95 | 11.3 | 886 | 98 | 11.1 | 0.8630 | 0.98 ( 0.75, | 1.27) | 0.97 ( 0.72, | 1.31) | 0.00 (-0.03, | 0.03) | |
| Region | | | | | | | | | | | | | | 0.6209 |
| North America | 161 | 35 | 21.7 | 159 | 32 | 20.1 | 0.7228 | 0.93 ( 0.60, | 1.42) | 0.91 ( 0.53, | 1.56) | -0.02 (-0.11, | 0.07) | |
| Latin America | 420 | 46 | 11.0 | 440 | 41 | 9.3 | 0.4269 | 0.85 ( 0.57, | 1.27) | 0.84 ( 0.54, | 1.30) | -0.02 (-0.06, | 0.02) | |
| Europe | 469 | 47 | 10.0 | 467 | 44 | 9.4 | 0.7569 | 0.94 ( 0.64, | 1.39) | 0.93 ( 0.61, | 1.44) | -0.01 (-0.04, | 0.03) | |
| Asia | 174 | 15 | 8.6 | 165 | 17 | 10.3 | 0.5964 | 1.20 ( 0.62, | 2.31) | 1.22 ( 0.59, | 2.53) | 0.02 (-0.05, | 0.08) | |
| Other | 50 | 1 | 2.0 | 47 | 4 | 8.5 | 0.1472 | 4.26 ( 0.49, | 36.71) | 4.56 ( 0.49, | 42.36) | 0.07 (-0.02, | 0.15) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0425 |
| Diabetic | 694 | 70 | 10.1 | 698 | 83 | 11.9 | 0.2818 | 1.18 ( 0.87, | 1.59) | 1.20 ( 0.86, | 1.69) | 0.02 (-0.01, | 0.05) | |
| Non-Diabetic | 580 | 74 | 12.8 | 580 | 55 | 9.5 | 0.0760 | 0.74 ( 0.53, | 1.03) | 0.72 ( 0.49, | 1.04) | -0.03 (-0.07, | 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2128 |
| <30 | 889 | 97 | 10.9 | 836 | 96 | 11.5 | 0.7064 | 1.05 ( 0.81, | 1.37) | 1.06 ( 0.79, | 1.43) | 0.01 (-0.02, | 0.04) | |
| >=30 | 385 | 47 | 12.2 | 442 | 42 | 9.5 | 0.2104 | 0.78 ( 0.53, | 1.15) | 0.76 ( 0.49, | 1.17) | -0.03 (-0.07, | 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1420 |
| <130 | 857 | 108 | 12.6 | 834 | 111 | 13.3 | 0.6650 | 1.06 ( 0.82, | 1.35) | 1.06 ( 0.80, | 1.41) | 0.01 (-0.02, | 0.04) | |
| >=130 | 417 | 36 | 8.6 | 444 | 27 | 6.1 | 0.1507 | 0.70 ( 0.44, | 1.14) | 0.69 ( 0.41, | 1.15) | -0.03 (-0.06, | 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9405 |
| <75 | 718 | 98 | 13.6 | 678 | 89 | 13.1 | 0.7747 | 0.96 ( 0.74, | 1.26) | 0.96 ( 0.70, | 1.30) | -0.01 (-0.04, | 0.03) | |
| 75 to <85 | 348 | 31 | 8.9 | 382 | 35 | 9.2 | 0.9048 | 1.03 ( 0.65, | 1.63) | 1.03 ( 0.62, | 1.71) | 0.00 (-0.04, | 0.04) | |
| >=85 | 208 | 15 | 7.2 | 218 | 14 | 6.4 | 0.7464 | 0.89 ( 0.44, | 1.80) | 0.88 ( 0.42, | 1.88) | -0.01 (-0.06, | 0.04) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0348 |
| <30 | 89 | 15 | 16.9 | 115 | 13 | 11.3 | 0.2533 | 0.67 | ( 0.34, 1.34) | 0.63 | ( 0.28, 1.40) | -0.06 | (-0.15, 0.04) | |
| 30 to <45 | 348 | 53 | 15.2 | 345 | 35 | 10.1 | 0.0444 | 0.67 | ( 0.45, 0.99) | 0.63 | ( 0.40, 0.99) | -0.05 | (-0.10, 0.00) | |
| >=45 | 837 | 76 | 9.1 | 818 | 90 | 11.0 | 0.1931 | 1.21 | ( 0.91, 1.62) | 1.24 | ( 0.90, 1.71) | 0.02 | (-0.01, 0.05) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5351 |
| Normal (<30) | 452 | 52 | 11.5 | 456 | 54 | 11.8 | 0.8741 | 1.03 | ( 0.72, 1.47) | 1.03 | ( 0.69, 1.55) | 0.00 | (-0.04, 0.05) | |
| Microalbuminuria (30 to <=300) | 627 | 72 | 11.5 | 608 | 69 | 11.3 | 0.9407 | 0.99 | ( 0.72, 1.35) | 0.99 | ( 0.69, 1.40) | 0.00 | (-0.04, 0.03) | |
| Macroalbuminuria (>300) | 189 | 20 | 10.6 | 207 | 15 | 7.2 | 0.2428 | 0.68 | ( 0.36, 1.30) | 0.66 | ( 0.33, 1.33) | -0.03 | (-0.09, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0113 |
| Low, moderate or high | 953 | 93 | 9.8 | 947 | 106 | 11.2 | 0.3072 | 1.15 | ( 0.88, 1.49) | 1.17 | ( 0.87, 1.56) | 0.01 | (-0.01, 0.04) | |
| Very high | 315 | 51 | 16.2 | 325 | 32 | 9.8 | 0.0169 | 0.61 | ( 0.40, 0.92) | 0.57 | ( 0.35, 0.91) | -0.06 | (-0.12,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5791 |
| No | 161 | 19 | 11.8 | 168 | 22 | 13.1 | 0.7224 | 1.11 | ( 0.62, 1.97) | 1.13 | ( 0.58, 2.17) | 0.01 | (-0.06, 0.08) | |
| Yes | 1113 | 125 | 11.2 | 1110 | 116 | 10.5 | 0.5540 | 0.93 | ( 0.73, 1.18) | 0.92 | ( 0.71, 1.21) | -0.01 | (-0.03, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4406 |
| No | 62 | 9 | 14.5 | 72 | 7 | 9.7 | 0.3935 | 0.67 | ( 0.26, 1.69) | 0.63 | ( 0.22, 1.82) | -0.05 | (-0.16, 0.06) | |
| Yes | 1212 | 135 | 11.1 | 1206 | 131 | 10.9 | 0.8282 | 0.98 | ( 0.78, 1.22) | 0.97 | ( 0.75, 1.25) | 0.00 | (-0.03, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5322 |
| No | 46 | 5 | 10.9 | 57 | 4 | 7.0 | 0.4913 | 0.65 | ( 0.18, 2.27) | 0.62 | ( 0.16, 2.45) | -0.04 | (-0.15, 0.07) | |
| Yes | 1228 | 139 | 11.3 | 1221 | 134 | 11.0 | 0.7864 | 0.97 | ( 0.78, 1.21) | 0.97 | ( 0.75, 1.24) | 0.00 | (-0.03, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 184 | 14.4 | 1278 | 168 | 13.1 | 0.3420 | 0.91 ( 0.75, 1.11) | 0.90 ( 0.72, 1.12) | -0.01 (-0.04, 0.01) | |
| Sex | | | | | | | | | | | 0.7832 |
| Male | 958 | 137 | 14.3 | 975 | 125 | 12.8 | 0.3419 | 0.90 ( 0.72, 1.12) | 0.88 ( 0.68, 1.14) | -0.01 (-0.05, 0.02) | |
| Female | 316 | 47 | 14.9 | 303 | 43 | 14.2 | 0.8098 | 0.95 ( 0.65, 1.40) | 0.95 ( 0.61, 1.48) | -0.01 (-0.06, 0.05) | |
| Age [years] | | | | | | | | | | | 0.5256 |
| <65 | 435 | 69 | 15.9 | 392 | 52 | 13.3 | 0.2914 | 0.84 ( 0.60, 1.17) | 0.81 ( 0.55, 1.20) | -0.03 (-0.07, 0.02) | |
| >=65 | 839 | 115 | 13.7 | 886 | 116 | 13.1 | 0.7081 | 0.96 ( 0.75, 1.21) | 0.95 ( 0.72, 1.25) | -0.01 (-0.04, 0.03) | |
| Region | | | | | | | | | | | 0.3593 |
| North America | 161 | 23 | 14.3 | 159 | 29 | 18.2 | 0.3378 | 1.28 ( 0.77, 2.11) | 1.34 ( 0.74, 2.43) | 0.04 (-0.04, 0.12) | |
| Latin America | 420 | 62 | 14.8 | 440 | 53 | 12.0 | 0.2420 | 0.82 ( 0.58, 1.15) | 0.79 ( 0.53, 1.17) | -0.03 (-0.07, 0.02) | |
| Europe | 469 | 69 | 14.7 | 467 | 66 | 14.1 | 0.8008 | 0.96 ( 0.70, 1.31) | 0.95 ( 0.66, 1.37) | -0.01 (-0.05, 0.04) | |
| Asia | 174 | 23 | 13.2 | 165 | 18 | 10.9 | 0.5145 | 0.83 ( 0.46, 1.47) | 0.80 ( 0.42, 1.55) | -0.02 (-0.09, 0.05) | |
| Other | 50 | 7 | 14.0 | 47 | 2 | 4.3 | 0.0983 | 0.30 ( 0.07, 1.39) | 0.27 ( 0.05, 1.39) | -0.10 (-0.21, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.6762 |
| Diabetic | 694 | 100 | 14.4 | 698 | 95 | 13.6 | 0.6676 | 0.94 ( 0.73, 1.23) | 0.94 ( 0.69, 1.27) | -0.01 (-0.04, 0.03) | |
| Non-Diabetic | 580 | 84 | 14.5 | 580 | 73 | 12.6 | 0.3451 | 0.87 ( 0.65, 1.16) | 0.85 ( 0.61, 1.19) | -0.02 (-0.06, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.6284 |
| <30 | 889 | 114 | 12.8 | 836 | 100 | 12.0 | 0.5874 | 0.93 ( 0.73, 1.20) | 0.92 ( 0.69, 1.23) | -0.01 (-0.04, 0.02) | |
| >=30 | 385 | 70 | 18.2 | 442 | 68 | 15.4 | 0.2819 | 0.85 ( 0.62, 1.15) | 0.82 ( 0.57, 1.18) | -0.03 (-0.08, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.0412 |
| <130 | 857 | 132 | 15.4 | 834 | 101 | 12.1 | 0.0496 | 0.79 ( 0.62, >1.00) | 0.76 ( 0.57, 1.00) | -0.03 (-0.07, 0.00) | |
| >=130 | 417 | 52 | 12.5 | 444 | 67 | 15.1 | 0.2656 | 1.21 ( 0.86, 1.69) | 1.25 ( 0.84, 1.84) | 0.03 (-0.02, 0.07) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.3586 |
| <75 | 718 | 111 | 15.5 | 678 | 101 | 14.9 | 0.7696 | 0.96 ( 0.75, 1.24) | 0.96 ( 0.71, 1.28) | -0.01 (-0.04, 0.03) | |
| 75 to <85 | 348 | 50 | 14.4 | 382 | 40 | 10.5 | 0.1097 | 0.73 ( 0.49, 1.08) | 0.70 ( 0.45, 1.09) | -0.04 (-0.09, 0.01) | |
| >=85 | 208 | 23 | 11.1 | 218 | 27 | 12.4 | 0.6704 | 1.12 ( 0.66, 1.89) | 1.14 ( 0.63, 2.05) | 0.01 (-0.05, 0.07) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3245 |
| <30 | 89 | 17 | 19.1 | 115 | 28 | 24.3 | 0.3701 | 1.27 ( 0.75, 2.18) | 1.36 ( 0.69, 2.69) | 0.05 (-0.06, 0.17) | |
| 30 to <45 | 348 | 62 | 17.8 | 345 | 57 | 16.5 | 0.6515 | 0.93 ( 0.67, 1.29) | 0.91 ( 0.61, 1.36) | -0.01 (-0.07, 0.04) | |
| >=45 | 837 | 105 | 12.5 | 818 | 83 | 10.1 | 0.1243 | 0.81 ( 0.62, 1.06) | 0.79 ( 0.58, 1.07) | -0.02 (-0.05, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.7666 |
| Normal (<30) | 452 | 62 | 13.7 | 456 | 55 | 12.1 | 0.4566 | 0.88 ( 0.63, 1.23) | 0.86 ( 0.58, 1.27) | -0.02 (-0.06, 0.03) | |
| Microalbuminuria (30 to <=300) | 627 | 91 | 14.5 | 608 | 79 | 13.0 | 0.4382 | 0.90 ( 0.68, 1.18) | 0.88 ( 0.64, 1.22) | -0.02 (-0.05, 0.02) | |
| Macroalbuminuria (>300) | 189 | 29 | 15.3 | 207 | 34 | 16.4 | 0.7689 | 1.07 ( 0.68, 1.69) | 1.08 ( 0.63, 1.86) | 0.01 (-0.06, 0.08) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0589 |
| Low, moderate or high | 953 | 126 | 13.2 | 947 | 100 | 10.6 | 0.0731 | 0.80 ( 0.62, 1.02) | 0.77 ( 0.59, 1.02) | -0.03 (-0.06, 0.00) | |
| Very high | 315 | 56 | 17.8 | 325 | 68 | 20.9 | 0.3142 | 1.18 ( 0.86, 1.62) | 1.22 ( 0.83, 1.81) | 0.03 (-0.03, 0.09) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.8291 |
| No | 161 | 25 | 15.5 | 168 | 25 | 14.9 | 0.8702 | 0.96 ( 0.58, 1.60) | 0.95 ( 0.52, 1.74) | -0.01 (-0.08, 0.07) | |
| Yes | 1113 | 159 | 14.3 | 1110 | 143 | 12.9 | 0.3344 | 0.90 ( 0.73, 1.11) | 0.89 ( 0.70, 1.13) | -0.01 (-0.04, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.2320 |
| No | 62 | 10 | 16.1 | 72 | 6 | 8.3 | 0.1653 | 0.52 ( 0.20, 1.34) | 0.47 ( 0.16, 1.39) | -0.08 (-0.19, 0.03) | |
| Yes | 1212 | 174 | 14.4 | 1206 | 162 | 13.4 | 0.5115 | 0.94 ( 0.77, 1.14) | 0.93 ( 0.74, 1.17) | -0.01 (-0.04, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.5057 |
| No | 46 | 5 | 10.9 | 57 | 8 | 14.0 | 0.6306 | 1.29 ( 0.45, 3.68) | 1.34 ( 0.41, 4.41) | 0.03 (-0.10, 0.16) | |
| Yes | 1228 | 179 | 14.6 | 1221 | 160 | 13.1 | 0.2914 | 0.90 ( 0.74, 1.10) | 0.88 ( 0.70, 1.11) | -0.01 (-0.04, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 46 | 3.6 | 1278 | 39 | 3.1 | 0.4313 | 0.85 ( 0.56, | 1.29) | 0.84 ( 0.54, | 1.30) | -0.01 (-0.02, | 0.01) | |
| Sex | | | | | | | | | | | | | | 0.4740 |
| Male | 958 | 40 | 4.2 | 975 | 36 | 3.7 | 0.5848 | 0.88 ( 0.57, | 1.37) | 0.88 ( 0.56, | 1.39) | 0.00 (-0.02, | 0.01) | |
| Female | 316 | 6 | 1.9 | 303 | 3 | 1.0 | 0.3451 | 0.52 ( 0.13, | 2.07) | 0.52 ( 0.13, | 2.08) | -0.01 (-0.03, | 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.0293 |
| <65 | 435 | 17 | 3.9 | 392 | 5 | 1.3 | 0.0188 | 0.33 ( 0.12, | 0.88) | 0.32 ( 0.12, | 0.87) | -0.03 (-0.05, | 0.00) | |
| >=65 | 839 | 29 | 3.5 | 886 | 34 | 3.8 | 0.6733 | 1.11 ( 0.68, | 1.81) | 1.11 ( 0.67, | 1.85) | 0.00 (-0.01, | 0.02) | |
| Region | | | | | | | | | | | | | | 0.1508 |
| North America | 161 | 7 | 4.3 | 159 | 11 | 6.9 | 0.3184 | 1.59 ( 0.63, | 4.00) | 1.64 ( 0.62, | 4.33) | 0.03 (-0.02, | 0.08) | |
| Latin America | 420 | 4 | 1.0 | 440 | 3 | 0.7 | 0.6589 | 0.72 ( 0.16, | 3.18) | 0.71 ( 0.16, | 3.21) | 0.00 (-0.01, | 0.01) | |
| Europe | 469 | 20 | 4.3 | 467 | 20 | 4.3 | 0.9890 | 1.00 ( 0.55, | 1.84) | 1.00 ( 0.53, | 1.89) | 0.00 (-0.03, | 0.03) | |
| Asia | 174 | 15 | 8.6 | 165 | 4 | 2.4 | 0.0132 | 0.28 ( 0.10, | 0.83) | 0.26 ( 0.09, | 0.81) | -0.06 (-0.11,-0.01) | | |
| Other | 50 | 0 | 0 | 47 | 1 | 2.1 | 0.4484 | 3.19 ( 0.13, | 76.36) | 3.26 ( 0.13, | 81.98) | 0.02 (-0.03, | 0.08) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5895 |
| Diabetic | 694 | 25 | 3.6 | 698 | 19 | 2.7 | 0.3480 | 0.76 ( 0.42, | 1.36) | 0.75 ( 0.41, | 1.37) | -0.01 (-0.03, | 0.01) | |
| Non-Diabetic | 580 | 21 | 3.6 | 580 | 20 | 3.4 | 0.8737 | 0.95 ( 0.52, | 1.74) | 0.95 ( 0.51, | 1.77) | 0.00 (-0.02, | 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8118 |
| <30 | 889 | 36 | 4.0 | 836 | 30 | 3.6 | 0.6179 | 0.89 ( 0.55, | 1.43) | 0.88 ( 0.54, | 1.45) | 0.00 (-0.02, | 0.01) | |
| >=30 | 385 | 10 | 2.6 | 442 | 9 | 2.0 | 0.5910 | 0.78 ( 0.32, | 1.91) | 0.78 ( 0.31, | 1.94) | -0.01 (-0.03, | 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8457 |
| <130 | 857 | 33 | 3.9 | 834 | 28 | 3.4 | 0.5865 | 0.87 ( 0.53, | 1.43) | 0.87 ( 0.52, | 1.45) | 0.00 (-0.02, | 0.01) | |
| >=130 | 417 | 13 | 3.1 | 444 | 11 | 2.5 | 0.5686 | 0.79 ( 0.36, | 1.75) | 0.79 ( 0.35, | 1.78) | -0.01 (-0.03, | 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4683 |
| <75 | 718 | 31 | 4.3 | 678 | 30 | 4.4 | 0.9220 | 1.02 ( 0.63, | 1.67) | 1.03 ( 0.61, | 1.71) | 0.00 (-0.02, | 0.02) | |
| 75 to <85 | 348 | 5 | 1.4 | 382 | 3 | 0.8 | 0.3985 | 0.55 ( 0.13, | 2.27) | 0.54 ( 0.13, | 2.29) | -0.01 (-0.02, | 0.01) | |
| >=85 | 208 | 10 | 4.8 | 218 | 6 | 2.8 | 0.2647 | 0.57 ( 0.21, | 1.55) | 0.56 ( 0.20, | 1.57) | -0.02 (-0.06, | 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0634 |
| <30 | 89 | 1 | 1.1 | 115 | 10 | 8.7 | 0.0176 | 7.74 ( 1.01, 59.34) | 8.38 ( 1.05, 66.75) | 0.08 ( 0.02, 0.13) | |
| 30 to <45 | 348 | 22 | 6.3 | 345 | 13 | 3.8 | 0.1248 | 0.60 ( 0.31, 1.16) | 0.58 ( 0.29, 1.17) | -0.03 (-0.06, 0.01) | |
| >=45 | 837 | 23 | 2.7 | 818 | 16 | 2.0 | 0.2883 | 0.71 ( 0.38, 1.34) | 0.71 ( 0.37, 1.35) | -0.01 (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.6522 |
| Normal (<30) | 452 | 16 | 3.5 | 456 | 17 | 3.7 | 0.8795 | 1.05 ( 0.54, 2.06) | 1.06 ( 0.53, 2.12) | 0.00 (-0.02, 0.03) | |
| Microalbuminuria (30 to <=300) | 627 | 24 | 3.8 | 608 | 16 | 2.6 | 0.2352 | 0.69 ( 0.37, 1.28) | 0.68 ( 0.36, 1.29) | -0.01 (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 189 | 6 | 3.2 | 207 | 6 | 2.9 | 0.8728 | 0.91 ( 0.30, 2.78) | 0.91 ( 0.29, 2.87) | 0.00 (-0.04, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.4467 |
| Low, moderate or high | 953 | 30 | 3.1 | 947 | 22 | 2.3 | 0.2705 | 0.74 ( 0.43, 1.27) | 0.73 ( 0.42, 1.28) | -0.01 (-0.02, 0.01) | |
| Very high | 315 | 16 | 5.1 | 325 | 17 | 5.2 | 0.9310 | 1.03 ( 0.53, 2.00) | 1.03 ( 0.51, 2.08) | 0.00 (-0.03, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.7510 |
| No | 161 | 9 | 5.6 | 168 | 9 | 5.4 | 0.9260 | 0.96 ( 0.39, 2.35) | 0.96 ( 0.37, 2.47) | 0.00 (-0.05, 0.05) | |
| Yes | 1113 | 37 | 3.3 | 1110 | 30 | 2.7 | 0.3914 | 0.81 ( 0.51, 1.31) | 0.81 ( 0.50, 1.32) | -0.01 (-0.02, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.5693 |
| No | 62 | 2 | 3.2 | 72 | 1 | 1.4 | 0.4736 | 0.43 ( 0.04, 4.64) | 0.42 ( 0.04, 4.78) | -0.02 (-0.07, 0.03) | |
| Yes | 1212 | 44 | 3.6 | 1206 | 38 | 3.2 | 0.5149 | 0.87 ( 0.57, 1.33) | 0.86 ( 0.56, 1.34) | 0.00 (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.4738 |
| No | 46 | 1 | 2.2 | 57 | 0 | 0 | 0.3852 | 0.27 ( 0.01, 6.48) | 0.26 ( 0.01, 6.63) | -0.02 (-0.08, 0.03) | |
| Yes | 1228 | 45 | 3.7 | 1221 | 39 | 3.2 | 0.5225 | 0.87 ( 0.57, 1.33) | 0.87 ( 0.56, 1.34) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 10 | 0.8 | 1278 | 7 | 0.5 | 0.4614 | 0.70 ( 0.27, 1.83) | 0.70 ( 0.26, 1.83) | 0.00 (-0.01, 0.00) | |
| Sex | | | | | | | | | | | 0.1499 |
| Male | 958 | 10 | 1.0 | 975 | 5 | 0.5 | 0.1834 | 0.49 ( 0.17, 1.43) | 0.49 ( 0.17, 1.43) | -0.01 (-0.01, 0.00) | |
| Female | 316 | 0 | 0 | 303 | 2 | 0.7 | 0.2324 | 5.21 ( 0.25,108.16) | 5.25 ( 0.25,109.78) | 0.01 ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | 0.7815 |
| <65 | 435 | 4 | 0.9 | 392 | 3 | 0.8 | 0.8090 | 0.83 ( 0.19, 3.70) | 0.83 ( 0.18, 3.74) | 0.00 (-0.01, 0.01) | |
| >=65 | 839 | 6 | 0.7 | 886 | 4 | 0.5 | 0.4709 | 0.63 ( 0.18, 2.23) | 0.63 ( 0.18, 2.24) | 0.00 (-0.01, 0.00) | |
| Region | | | | | | | | | | | |
| North America | 161 | 2 | 1.2 | 159 | 3 | 1.9 | | | | | |
| Latin America | 420 | 2 | 0.5 | 440 | 3 | 0.7 | | | | | |
| Europe | 469 | 1 | 0.2 | 467 | 1 | 0.2 | | | | | |
| Asia | 174 | 3 | 1.7 | 165 | 0 | 0 | | | | | |
| Other | 50 | 2 | 4.0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | 0.8602 |
| Diabetic | 694 | 10 | 1.4 | 698 | 7 | 1.0 | 0.4569 | 0.70 ( 0.27, 1.82) | 0.69 ( 0.26, 1.83) | 0.00 (-0.02, 0.01) | |
| Non-Diabetic | 580 | 0 | 0 | 580 | 0 | 0 | 1.0000 | 1.00 ( 0.02, 50.31) | 1.00 ( 0.02, 50.48) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.1880 |
| <30 | 889 | 9 | 1.0 | 836 | 4 | 0.5 | 0.2000 | 0.47 ( 0.15, 1.53) | 0.47 ( 0.14, 1.53) | -0.01 (-0.01, 0.00) | |
| >=30 | 385 | 1 | 0.3 | 442 | 3 | 0.7 | 0.3863 | 2.61 ( 0.27, 25.02) | 2.62 ( 0.27, 25.33) | 0.00 ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 6 | 0.7 | 834 | 3 | 0.4 | | | | | |
| >=130 | 417 | 4 | 1.0 | 444 | 4 | 0.9 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 5 | 0.7 | 678 | 3 | 0.4 | | | | | |
| 75 to <85 | 348 | 3 | 0.9 | 382 | 3 | 0.8 | | | | | |
| >=85 | 208 | 2 | 1.0 | 218 | 1 | 0.5 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 2 | 1.7 | | | | | |
| 30 to <45 | 348 | 4 | 1.1 | 345 | 2 | 0.6 | | | | | |
| >=45 | 837 | 6 | 0.7 | 818 | 3 | 0.4 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 1 | 0.2 | 456 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 4 | 0.6 | 608 | 2 | 0.3 | | | | | |
| Macroalbuminuria (>300) | 189 | 5 | 2.6 | 207 | 4 | 1.9 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.2845 |
| Low, moderate or high | 953 | 7 | 0.7 | 947 | 3 | 0.3 | 0.2083 | 0.43 ( 0.11, 1.66) | 0.43 ( 0.11, 1.67) | 0.00 (-0.01, 0.00) | |
| Very high | 315 | 3 | 1.0 | 325 | 4 | 1.2 | 0.7350 | 1.29 ( 0.29, 5.73) | 1.30 ( 0.29, 5.84) | 0.00 (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.4381 |
| No | 161 | 3 | 1.9 | 168 | 1 | 0.6 | 0.2941 | 0.32 ( 0.03, 3.04) | 0.32 ( 0.03, 3.06) | -0.01 (-0.04, 0.01) | |
| Yes | 1113 | 7 | 0.6 | 1110 | 6 | 0.5 | 0.7846 | 0.86 ( 0.29, 2.55) | 0.86 ( 0.29, 2.56) | 0.00 (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.3160 |
| No | 62 | 2 | 3.2 | 72 | 0 | 0 | 0.1936 | 0.17 (<0.01, 3.53) | 0.17 (<0.01, 3.54) | -0.03 (-0.08, 0.02) | |
| Yes | 1212 | 8 | 0.7 | 1206 | 7 | 0.6 | 0.8031 | 0.88 ( 0.32, 2.42) | 0.88 ( 0.32, 2.43) | 0.00 (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.5310 |
| No | 46 | 1 | 2.2 | 57 | 0 | 0 | 0.3852 | 0.27 ( 0.01, 6.48) | 0.26 ( 0.01, 6.63) | -0.02 (-0.08, 0.03) | |
| Yes | 1228 | 9 | 0.7 | 1221 | 7 | 0.6 | 0.6240 | 0.78 ( 0.29, 2.09) | 0.78 ( 0.29, 2.10) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 122 | 9.6 | 1278 | 93 | 7.3 | 0.0365 | 0.76 ( 0.59, | 0.98) | 0.74 ( 0.56, | 0.98) | -0.02 (-0.04, | 0.00) | |
| Sex | | | | | | | | | | | | | | 0.5573 |
| Male | 958 | 89 | 9.3 | 975 | 72 | 7.4 | 0.1295 | 0.79 ( 0.59, | 1.07) | 0.78 ( 0.56, | 1.08) | -0.02 (-0.04, | 0.01) | |
| Female | 316 | 33 | 10.4 | 303 | 21 | 6.9 | 0.1216 | 0.66 ( 0.39, | 1.12) | 0.64 ( 0.36, | 1.13) | -0.04 (-0.08, | 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6816 |
| <65 | 435 | 37 | 8.5 | 392 | 23 | 5.9 | 0.1441 | 0.69 ( 0.42, | 1.14) | 0.67 ( 0.39, | 1.15) | -0.03 (-0.06, | 0.01) | |
| >=65 | 839 | 85 | 10.1 | 886 | 70 | 7.9 | 0.1054 | 0.78 ( 0.58, | 1.05) | 0.76 ( 0.55, | 1.06) | -0.02 (-0.05, | 0.00) | |
| Region | | | | | | | | | | | | | | 0.9462 |
| North America | 161 | 13 | 8.1 | 159 | 12 | 7.5 | 0.8605 | 0.93 ( 0.44, | 1.99) | 0.93 ( 0.41, | 2.10) | -0.01 (-0.06, | 0.05) | |
| Latin America | 420 | 40 | 9.5 | 440 | 31 | 7.0 | 0.1868 | 0.74 ( 0.47, | 1.16) | 0.72 ( 0.44, | 1.17) | -0.02 (-0.06, | 0.01) | |
| Europe | 469 | 43 | 9.2 | 467 | 32 | 6.9 | 0.1919 | 0.75 ( 0.48, | 1.16) | 0.73 ( 0.45, | 1.17) | -0.02 (-0.06, | 0.01) | |
| Asia | 174 | 18 | 10.3 | 165 | 14 | 8.5 | 0.5583 | 0.82 ( 0.42, | 1.60) | 0.80 ( 0.39, | 1.67) | -0.02 (-0.08, | 0.04) | |
| Other | 50 | 8 | 16.0 | 47 | 4 | 8.5 | 0.2629 | 0.53 ( 0.17, | 1.65) | 0.49 ( 0.14, | 1.74) | -0.07 (-0.20, | 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9703 |
| Diabetic | 694 | 73 | 10.5 | 698 | 56 | 8.0 | 0.1084 | 0.76 ( 0.55, | 1.06) | 0.74 ( 0.51, | 1.07) | -0.02 (-0.06, | 0.01) | |
| Non-Diabetic | 580 | 49 | 8.4 | 580 | 37 | 6.4 | 0.1787 | 0.76 ( 0.50, | 1.14) | 0.74 ( 0.47, | 1.15) | -0.02 (-0.05, | 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6750 |
| <30 | 889 | 86 | 9.7 | 836 | 64 | 7.7 | 0.1371 | 0.79 ( 0.58, | 1.08) | 0.77 ( 0.55, | 1.09) | -0.02 (-0.05, | 0.01) | |
| >=30 | 385 | 36 | 9.4 | 442 | 29 | 6.6 | 0.1370 | 0.70 ( 0.44, | 1.12) | 0.68 ( 0.41, | 1.13) | -0.03 (-0.07, | 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7894 |
| <130 | 857 | 73 | 8.5 | 834 | 52 | 6.2 | 0.0728 | 0.73 ( 0.52, | 1.03) | 0.71 ( 0.49, | 1.03) | -0.02 (-0.05, | 0.00) | |
| >=130 | 417 | 49 | 11.8 | 444 | 41 | 9.2 | 0.2278 | 0.79 ( 0.53, | 1.16) | 0.76 ( 0.49, | 1.18) | -0.03 (-0.07, | 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5727 |
| <75 | 718 | 75 | 10.4 | 678 | 58 | 8.6 | 0.2290 | 0.82 ( 0.59, | 1.13) | 0.80 ( 0.56, | 1.15) | -0.02 (-0.05, | 0.01) | |
| 75 to <85 | 348 | 28 | 8.0 | 382 | 18 | 4.7 | 0.0641 | 0.59 ( 0.33, | 1.04) | 0.57 ( 0.31, | 1.04) | -0.03 (-0.07, | 0.00) | |
| >=85 | 208 | 19 | 9.1 | 218 | 17 | 7.8 | 0.6201 | 0.85 ( 0.46, | 1.60) | 0.84 ( 0.42, | 1.67) | -0.01 (-0.07, | 0.04) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.4513 |
| <30 | 89 | 14 | 15.7 | 115 | 15 | 13.0 | 0.5858 | 0.83 ( 0.42, | 1.63) | 0.80 ( 0.37, | 1.77) | -0.03 (-0.12, 0.07) | |
| 30 to <45 | 348 | 49 | 14.1 | 345 | 29 | 8.4 | 0.0181 | 0.60 ( 0.39, | 0.92) | 0.56 ( 0.34, | 0.91) | -0.06 (-0.10,-0.01) | |
| >=45 | 837 | 59 | 7.0 | 818 | 49 | 6.0 | 0.3832 | 0.85 ( 0.59, | 1.23) | 0.84 ( 0.57, | 1.24) | -0.01 (-0.03, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.8315 |
| Normal (<30) | 452 | 48 | 10.6 | 456 | 36 | 7.9 | 0.1565 | 0.74 ( 0.49, | 1.12) | 0.72 ( 0.46, | 1.14) | -0.03 (-0.06, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 53 | 8.5 | 608 | 42 | 6.9 | 0.3083 | 0.82 ( 0.55, | 1.21) | 0.80 ( 0.53, | 1.22) | -0.02 (-0.05, 0.01) | |
| Macroalbuminuria (>300) | 189 | 21 | 11.1 | 207 | 15 | 7.2 | 0.1815 | 0.65 ( 0.35, | 1.23) | 0.63 ( 0.31, | 1.25) | -0.04 (-0.10, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.4790 |
| Low, moderate or high | 953 | 73 | 7.7 | 947 | 59 | 6.2 | 0.2203 | 0.81 ( 0.58, | 1.13) | 0.80 ( 0.56, | 1.14) | -0.01 (-0.04, 0.01) | |
| Very high | 315 | 49 | 15.6 | 325 | 34 | 10.5 | 0.0551 | 0.67 ( 0.45, | 1.01) | 0.63 ( 0.40, | 1.01) | -0.05 (-0.10, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.4024 |
| No | 161 | 11 | 6.8 | 168 | 12 | 7.1 | 0.9121 | 1.05 ( 0.47, | 2.30) | 1.05 ( 0.45, | 2.45) | 0.00 (-0.05, 0.06) | |
| Yes | 1113 | 111 | 10.0 | 1110 | 81 | 7.3 | 0.0247 | 0.73 ( 0.56, | 0.96) | 0.71 ( 0.53, | 0.96) | -0.03 (-0.05, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.1506 |
| No | 62 | 4 | 6.5 | 72 | 8 | 11.1 | 0.3463 | 1.72 ( 0.54, | 5.45) | 1.81 ( 0.52, | 6.34) | 0.05 (-0.05, 0.14) | |
| Yes | 1212 | 118 | 9.7 | 1206 | 85 | 7.0 | 0.0172 | 0.72 ( 0.55, | 0.95) | 0.70 ( 0.53, | 0.94) | -0.03 (-0.05, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.4077 |
| No | 46 | 3 | 6.5 | 57 | 5 | 8.8 | 0.6714 | 1.35 ( 0.34, | 5.33) | 1.38 ( 0.31, | 6.10) | 0.02 (-0.08, 0.12) | |
| Yes | 1228 | 119 | 9.7 | 1221 | 88 | 7.2 | 0.0272 | 0.74 ( 0.57, | 0.97) | 0.72 ( 0.54, | 0.97) | -0.02 (-0.05, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 9 | 0.7 | 1278 | 13 | 1.0 | 0.3958 | 1.44 ( 0.62, 3.36) | 1.44 ( 0.62, 3.39) | 0.00 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | 0.3602 |
| Male | 958 | 6 | 0.6 | 975 | 11 | 1.1 | 0.2373 | 1.80 ( 0.67, 4.85) | 1.81 ( 0.67, 4.92) | 0.01 ( 0.00, 0.01) | |
| Female | 316 | 3 | 0.9 | 303 | 2 | 0.7 | 0.6877 | 0.70 ( 0.12, 4.13) | 0.69 ( 0.12, 4.18) | 0.00 (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | 0.4361 |
| <65 | 435 | 3 | 0.7 | 392 | 6 | 1.5 | 0.2445 | 2.22 ( 0.56, 8.81) | 2.24 ( 0.56, 9.01) | 0.01 (-0.01, 0.02) | |
| >=65 | 839 | 6 | 0.7 | 886 | 7 | 0.8 | 0.8573 | 1.10 ( 0.37, 3.27) | 1.11 ( 0.37, 3.30) | 0.00 (-0.01, 0.01) | |
| Region | | | | | | | | | | | 0.9099 |
| North America | 161 | 1 | 0.6 | 159 | 1 | 0.6 | 0.9929 | 1.01 ( 0.06, 16.05) | 1.01 ( 0.06, 16.33) | 0.00 (-0.02, 0.02) | |
| Latin America | 420 | 3 | 0.7 | 440 | 6 | 1.4 | 0.3496 | 1.91 ( 0.48, 7.58) | 1.92 ( 0.48, 7.73) | 0.01 (-0.01, 0.02) | |
| Europe | 469 | 4 | 0.9 | 467 | 6 | 1.3 | 0.5204 | 1.51 ( 0.43, 5.30) | 1.51 ( 0.42, 5.40) | 0.00 (-0.01, 0.02) | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | 0.9789 | 1.05 ( 0.02, 52.82) | 1.05 ( 0.02, 53.44) | 0.00 (-0.01, 0.01) | |
| Other | 50 | 1 | 2.0 | 47 | 0 | 0 | 0.5020 | 0.35 ( 0.01, 8.48) | 0.35 ( 0.01, 8.74) | -0.02 (-0.07, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.7876 |
| Diabetic | 694 | 8 | 1.2 | 698 | 12 | 1.7 | 0.3746 | 1.49 ( 0.61, 3.63) | 1.50 ( 0.61, 3.69) | 0.01 (-0.01, 0.02) | |
| Non-Diabetic | 580 | 1 | 0.2 | 580 | 1 | 0.2 | 1.0000 | 1.00 ( 0.06, 15.95) | 1.00 ( 0.06, 16.03) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.1319 |
| <30 | 889 | 3 | 0.3 | 836 | 8 | 1.0 | 0.1062 | 2.84 ( 0.75, 10.65) | 2.85 ( 0.75, 10.79) | 0.01 ( 0.00, 0.01) | |
| >=30 | 385 | 6 | 1.6 | 442 | 5 | 1.1 | 0.5927 | 0.73 ( 0.22, 2.36) | 0.72 ( 0.22, 2.39) | 0.00 (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.9807 |
| <130 | 857 | 5 | 0.6 | 834 | 7 | 0.8 | 0.5308 | 1.44 ( 0.46, 4.51) | 1.44 ( 0.46, 4.56) | 0.00 (-0.01, 0.01) | |
| >=130 | 417 | 4 | 1.0 | 444 | 6 | 1.4 | 0.5915 | 1.41 ( 0.40, 4.96) | 1.41 ( 0.40, 5.05) | 0.00 (-0.01, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.2663 |
| <75 | 718 | 3 | 0.4 | 678 | 8 | 1.2 | 0.1075 | 2.82 ( 0.75, 10.60) | 2.85 ( 0.75, 10.77) | 0.01 ( 0.00, 0.02) | |
| 75 to <85 | 348 | 2 | 0.6 | 382 | 3 | 0.8 | 0.7304 | 1.37 ( 0.23, 8.13) | 1.37 ( 0.23, 8.24) | 0.00 (-0.01, 0.01) | |
| >=85 | 208 | 4 | 1.9 | 218 | 2 | 0.9 | 0.3786 | 0.48 ( 0.09, 2.58) | 0.47 ( 0.09, 2.61) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.9500 |
| <30 | 89 | 0 | 0 | 115 | 1 | 0.9 | 0.5923 | 2.33 ( 0.10, 56.46) | 2.34 ( 0.09, 58.25) | 0.01 (-0.02, 0.03) | |
| 30 to <45 | 348 | 3 | 0.9 | 345 | 4 | 1.2 | 0.6955 | 1.34 ( 0.30, 5.96) | 1.35 ( 0.30, 6.07) | 0.00 (-0.01, 0.02) | |
| >=45 | 837 | 6 | 0.7 | 818 | 8 | 1.0 | 0.5619 | 1.36 ( 0.48, 3.91) | 1.37 ( 0.47, 3.96) | 0.00 (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 2 | 0.4 | 456 | 3 | 0.7 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 4 | 0.6 | 608 | 5 | 0.8 | | | | | |
| Macroalbuminuria (>300) | 189 | 3 | 1.6 | 207 | 5 | 2.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.2763 |
| Low, moderate or high | 953 | 5 | 0.5 | 947 | 10 | 1.1 | 0.1907 | 2.01 ( 0.69, 5.87) | 2.02 ( 0.69, 5.94) | 0.01 ( 0.00, 0.01) | |
| Very high | 315 | 4 | 1.3 | 325 | 3 | 0.9 | 0.6733 | 0.73 ( 0.16, 3.22) | 0.72 ( 0.16, 3.26) | 0.00 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.1590 |
| No | 161 | 2 | 1.2 | 168 | 0 | 0 | 0.2313 | 0.19 (<0.01, 3.96) | 0.19 (<0.01, 3.97) | -0.01 (-0.03, 0.01) | |
| Yes | 1113 | 7 | 0.6 | 1110 | 13 | 1.2 | 0.1758 | 1.86 ( 0.75, 4.65) | 1.87 ( 0.74, 4.71) | 0.01 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.7043 |
| No | 62 | 1 | 1.6 | 72 | 1 | 1.4 | 0.9151 | 0.86 ( 0.05, 13.48) | 0.86 ( 0.05, 14.03) | 0.00 (-0.04, 0.04) | |
| Yes | 1212 | 8 | 0.7 | 1206 | 12 | 1.0 | 0.3632 | 1.51 ( 0.62, 3.67) | 1.51 ( 0.62, 3.71) | 0.00 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.2845 |
| No | 46 | 1 | 2.2 | 57 | 0 | 0 | 0.3852 | 0.27 ( 0.01, 6.48) | 0.26 ( 0.01, 6.63) | -0.02 (-0.08, 0.03) | |
| Yes | 1228 | 8 | 0.7 | 1221 | 13 | 1.1 | 0.2674 | 1.63 ( 0.68, 3.93) | 1.64 ( 0.68, 3.97) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 18 | 1.4 | 1278 | 13 | 1.0 | 0.3616 | 0.72 ( 0.35, 1.46) | 0.72 ( 0.35, 1.47) | 0.00 (-0.01, 0.00) | | |
| Sex | | | | | | | | | | | | 0.0886 |
| Male | 958 | 12 | 1.3 | 975 | 13 | 1.3 | 0.8752 | 1.06 ( 0.49, 2.32) | 1.07 ( 0.48, 2.35) | 0.00 (-0.01, 0.01) | | |
| Female | 316 | 6 | 1.9 | 303 | 0 | 0 | 0.0261 | 0.08 (<0.01, 1.42) | 0.08 (<0.01, 1.40) | -0.02 (-0.04, 0.00) | | |
| Age [years] | | | | | | | | | | | | 0.7578 |
| <65 | 435 | 4 | 0.9 | 392 | 2 | 0.5 | 0.4886 | 0.55 ( 0.10, 3.01) | 0.55 ( 0.10, 3.03) | 0.00 (-0.02, 0.01) | | |
| >=65 | 839 | 14 | 1.7 | 886 | 11 | 1.2 | 0.4581 | 0.74 ( 0.34, 1.63) | 0.74 ( 0.33, 1.64) | 0.00 (-0.02, 0.01) | | |
| Region | | | | | | | | | | | | 0.9922 |
| North America | 161 | 2 | 1.2 | 159 | 2 | 1.3 | 0.9900 | 1.01 ( 0.14, 7.10) | 1.01 ( 0.14, 7.28) | 0.00 (-0.02, 0.02) | | |
| Latin America | 420 | 4 | 1.0 | 440 | 3 | 0.7 | 0.6589 | 0.72 ( 0.16, 3.18) | 0.71 ( 0.16, 3.21) | 0.00 (-0.01, 0.01) | | |
| Europe | 469 | 5 | 1.1 | 467 | 4 | 0.9 | 0.7425 | 0.80 ( 0.22, 2.97) | 0.80 ( 0.21, 3.00) | 0.00 (-0.01, 0.01) | | |
| Asia | 174 | 7 | 4.0 | 165 | 4 | 2.4 | 0.4063 | 0.60 ( 0.18, 2.02) | 0.59 ( 0.17, 2.06) | -0.02 (-0.05, 0.02) | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 ( 0.02, 52.49) | 1.06 ( 0.02, 54.66) | 0.00 (-0.04, 0.04) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3512 |
| Diabetic | 694 | 8 | 1.2 | 698 | 8 | 1.1 | 0.9908 | 0.99 ( 0.38, 2.63) | 0.99 ( 0.37, 2.66) | 0.00 (-0.01, 0.01) | | |
| Non-Diabetic | 580 | 10 | 1.7 | 580 | 5 | 0.9 | 0.1938 | 0.50 ( 0.17, 1.45) | 0.50 ( 0.17, 1.46) | -0.01 (-0.02, 0.00) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1251 |
| <30 | 889 | 17 | 1.9 | 836 | 9 | 1.1 | 0.1545 | 0.56 ( 0.25, 1.26) | 0.56 ( 0.25, 1.26) | -0.01 (-0.02, 0.00) | | |
| >=30 | 385 | 1 | 0.3 | 442 | 4 | 0.9 | 0.2325 | 3.48 ( 0.39, 31.04) | 3.51 ( 0.39, 31.51) | 0.01 ( 0.00, 0.02) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.6866 |
| <130 | 857 | 13 | 1.5 | 834 | 10 | 1.2 | 0.5726 | 0.79 ( 0.35, 1.79) | 0.79 ( 0.34, 1.81) | 0.00 (-0.01, 0.01) | | |
| >=130 | 417 | 5 | 1.2 | 444 | 3 | 0.7 | 0.4238 | 0.56 ( 0.14, 2.34) | 0.56 ( 0.13, 2.36) | -0.01 (-0.02, 0.01) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2460 |
| <75 | 718 | 10 | 1.4 | 678 | 10 | 1.5 | 0.8973 | 1.06 ( 0.44, 2.53) | 1.06 ( 0.44, 2.56) | 0.00 (-0.01, 0.01) | | |
| 75 to <85 | 348 | 6 | 1.7 | 382 | 1 | 0.3 | 0.0429 | 0.15 ( 0.02, 1.25) | 0.15 ( 0.02, 1.25) | -0.01 (-0.03, 0.00) | | |
| >=85 | 208 | 2 | 1.0 | 218 | 2 | 0.9 | 0.9624 | 0.95 ( 0.14, 6.71) | 0.95 ( 0.13, 6.83) | 0.00 (-0.02, 0.02) | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0684 |
| <30 | 89 | 2 | 2.2 | 115 | 1 | 0.9 | 0.4176 | 0.39 ( 0.04, 4.20) | 0.38 ( 0.03, 4.28) | -0.01 (-0.05, 0.02) | |
| 30 to <45 | 348 | 1 | 0.3 | 345 | 6 | 1.7 | 0.0560 | 6.05 ( 0.73, 50.01) | 6.14 ( 0.74, 51.28) | 0.01 ( 0.00, 0.03) | |
| >=45 | 837 | 15 | 1.8 | 818 | 6 | 0.7 | 0.0544 | 0.41 ( 0.16, 1.05) | 0.40 ( 0.16, 1.05) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.7274 |
| Normal (<30) | 452 | 6 | 1.3 | 456 | 4 | 0.9 | 0.5157 | 0.66 ( 0.19, 2.33) | 0.66 ( 0.18, 2.35) | 0.00 (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 11 | 1.8 | 608 | 7 | 1.2 | 0.3766 | 0.66 ( 0.26, 1.68) | 0.65 ( 0.25, 1.69) | -0.01 (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 2 | 1.0 | 0.6163 | 1.83 ( 0.17, 19.98) | 1.83 ( 0.16, 20.39) | 0.00 (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.1931 |
| Low, moderate or high | 953 | 15 | 1.6 | 947 | 8 | 0.8 | 0.1461 | 0.54 ( 0.23, 1.26) | 0.53 ( 0.22, 1.26) | -0.01 (-0.02, 0.00) | |
| Very high | 315 | 3 | 1.0 | 325 | 5 | 1.5 | 0.5047 | 1.62 ( 0.39, 6.70) | 1.63 ( 0.39, 6.86) | 0.01 (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.5999 |
| No | 161 | 4 | 2.5 | 168 | 2 | 1.2 | 0.3806 | 0.48 ( 0.09, 2.58) | 0.47 ( 0.09, 2.62) | -0.01 (-0.04, 0.02) | |
| Yes | 1113 | 14 | 1.3 | 1110 | 11 | 1.0 | 0.5508 | 0.79 ( 0.36, 1.73) | 0.79 ( 0.36, 1.74) | 0.00 (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.3926 |
| No | 62 | 3 | 4.8 | 72 | 1 | 1.4 | 0.2420 | 0.29 ( 0.03, 2.69) | 0.28 ( 0.03, 2.73) | -0.03 (-0.09, 0.03) | |
| Yes | 1212 | 15 | 1.2 | 1206 | 12 | 1.0 | 0.5703 | 0.80 ( 0.38, 1.71) | 0.80 ( 0.37, 1.72) | 0.00 (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.5290 |
| No | 46 | 1 | 2.2 | 57 | 0 | 0 | 0.3852 | 0.27 ( 0.01, 6.48) | 0.26 ( 0.01, 6.63) | -0.02 (-0.08, 0.03) | |
| Yes | 1228 | 17 | 1.4 | 1221 | 13 | 1.1 | 0.4721 | 0.77 ( 0.38, 1.58) | 0.77 ( 0.37, 1.59) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 1 | 0.1 | 1278 | 0 | 0 | 0.4780 | 0.33 ( 0.01, 8.15) | 0.33 ( 0.01, 8.16) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 958 | 1 | 0.1 | 975 | 0 | 0 | | | | | |
| Female | 316 | 0 | 0 | 303 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 1 | 0.2 | 392 | 0 | 0 | | | | | |
| >=65 | 839 | 0 | 0 | 886 | 0 | 0 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 0 | 0 | | | | | |
| Latin America | 420 | 0 | 0 | 440 | 0 | 0 | | | | | |
| Europe | 469 | 0 | 0 | 467 | 0 | 0 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 1 | 0.1 | 698 | 0 | 0 | | | | | |
| Non-Diabetic | 580 | 0 | 0 | 580 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 1 | 0.1 | 836 | 0 | 0 | | | | | |
| >=30 | 385 | 0 | 0 | 442 | 0 | 0 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 0 | 0 | 834 | 0 | 0 | | | | | |
| >=130 | 417 | 1 | 0.2 | 444 | 0 | 0 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 0 | 0 | 678 | 0 | 0 | | | | | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 0 | 0 | | | | | |
| >=85 | 208 | 0 | 0 | 218 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 0 | 0 | | | | | |
| 30 to <45 | 348 | 0 | 0 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 1 | 0.1 | 818 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 0 | 0 | 456 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 0 | 0 | 608 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 1 | 0.1 | 947 | 0 | 0 | | | | | |
| Very high | 315 | 0 | 0 | 325 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 0 | 0 | 168 | 0 | 0 | | | | | |
| Yes | 1113 | 1 | 0.1 | 1110 | 0 | 0 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 0 | 0 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 1 | 0.1 | 1206 | 0 | 0 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 0 | 0 | | | | | |
| Yes | 1228 | 1 | 0.1 | 1221 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 7 | 0.5 | 1278 | 8 | 0.6 | 0.8004 | 1.14 ( 0.41, 3.13) | 1.14 ( 0.41, 3.15) | 0.00 (-0.01, 0.01) | |
| Sex | | | | | | | | | | | 0.1480 |
| Male | 958 | 7 | 0.7 | 975 | 5 | 0.5 | 0.5420 | 0.70 ( 0.22, 2.20) | 0.70 ( 0.22, 2.21) | 0.00 (-0.01, 0.00) | |
| Female | 316 | 0 | 0 | 303 | 3 | 1.0 | 0.1218 | 7.30 ( 0.38,140.72) | 7.37 ( 0.38,143.33) | 0.01 ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | 0.6105 |
| <65 | 435 | 2 | 0.5 | 392 | 3 | 0.8 | 0.5714 | 1.66 ( 0.28, 9.91) | 1.67 ( 0.28, 10.04) | 0.00 (-0.01, 0.01) | |
| >=65 | 839 | 5 | 0.6 | 886 | 5 | 0.6 | 0.9311 | 0.95 ( 0.28, 3.26) | 0.95 ( 0.27, 3.28) | 0.00 (-0.01, 0.01) | |
| Region | | | | | | | | | | | |
| North America | 161 | 2 | 1.2 | 159 | 3 | 1.9 | | | | | |
| Latin America | 420 | 2 | 0.5 | 440 | 4 | 0.9 | | | | | |
| Europe | 469 | 2 | 0.4 | 467 | 1 | 0.2 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | |
| Other | 50 | 1 | 2.0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | 0.9506 |
| Diabetic | 694 | 7 | 1.0 | 698 | 8 | 1.1 | 0.8038 | 1.14 ( 0.41, 3.12) | 1.14 ( 0.41, 3.16) | 0.00 (-0.01, 0.01) | |
| Non-Diabetic | 580 | 0 | 0 | 580 | 0 | 0 | 1.0000 | 1.00 ( 0.02, 50.31) | 1.00 ( 0.02, 50.48) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 5 | 0.6 | 836 | 4 | 0.5 | | | | | |
| >=30 | 385 | 2 | 0.5 | 442 | 4 | 0.9 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 5 | 0.6 | 834 | 3 | 0.4 | | | | | |
| >=130 | 417 | 2 | 0.5 | 444 | 5 | 1.1 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.4860 |
| <75 | 718 | 6 | 0.8 | 678 | 4 | 0.6 | 0.5864 | 0.71 ( 0.20, 2.49) | 0.70 ( 0.20, 2.51) | 0.00 (-0.01, 0.01) | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 3 | 0.8 | 0.3626 | 2.73 ( 0.29, 26.15) | 2.75 ( 0.28, 26.53) | 0.00 (-0.01, 0.02) | |
| >=85 | 208 | 0 | 0 | 218 | 1 | 0.5 | 0.4991 | 2.86 ( 0.12, 69.89) | 2.88 ( 0.12, 70.99) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 2 | 1.7 | | | | | |
| 30 to <45 | 348 | 3 | 0.9 | 345 | 3 | 0.9 | | | | | |
| >=45 | 837 | 4 | 0.5 | 818 | 3 | 0.4 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 2 | 0.4 | 456 | 2 | 0.4 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 4 | 0.6 | 608 | 2 | 0.3 | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 4 | 1.9 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.1731 |
| Low, moderate or high | 953 | 6 | 0.6 | 947 | 4 | 0.4 | 0.5326 | 0.67 ( 0.19, 2.37) | 0.67 ( 0.19, 2.38) | 0.00 (-0.01, 0.00) | |
| Very high | 315 | 1 | 0.3 | 325 | 4 | 1.2 | 0.1895 | 3.88 ( 0.44, 34.50) | 3.91 ( 0.43, 35.20) | 0.01 ( 0.00, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.5388 |
| No | 161 | 0 | 0 | 168 | 1 | 0.6 | 0.4969 | 2.88 ( 0.12, 70.08) | 2.89 ( 0.12, 71.52) | 0.01 (-0.01, 0.02) | |
| Yes | 1113 | 7 | 0.6 | 1110 | 7 | 0.6 | 0.9960 | 1.00 ( 0.35, 2.85) | 1.00 ( 0.35, 2.87) | 0.00 (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.1739 |
| No | 62 | 2 | 3.2 | 72 | 0 | 0 | 0.1936 | 0.17 (<0.01, 3.53) | 0.17 (<0.01, 3.54) | -0.03 (-0.08, 0.02) | |
| Yes | 1212 | 5 | 0.4 | 1206 | 8 | 0.7 | 0.3991 | 1.61 ( 0.53, 4.90) | 1.61 ( 0.53, 4.94) | 0.00 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.8650 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 ( 0.02, 40.07) | 0.81 ( 0.02, 41.54) | 0.00 (-0.04, 0.04) | |
| Yes | 1228 | 7 | 0.6 | 1221 | 8 | 0.7 | 0.7871 | 1.15 ( 0.42, 3.16) | 1.15 ( 0.42, 3.18) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 20 | 1.6 | 1278 | 20 | 1.6 | 0.9920 | 1.00 ( 0.54, 1.84) | 1.00 ( 0.53, 1.86) | 0.00 (-0.01, 0.01) | | |
| Sex | | | | | | | | | | | | 0.1581 |
| Male | 958 | 15 | 1.6 | 975 | 11 | 1.1 | 0.4037 | 0.72 ( 0.33, 1.56) | 0.72 ( 0.33, 1.57) | 0.00 (-0.01, 0.01) | | |
| Female | 316 | 5 | 1.6 | 303 | 9 | 3.0 | 0.2456 | 1.88 ( 0.64, 5.54) | 1.90 ( 0.63, 5.75) | 0.01 (-0.01, 0.04) | | |
| Age [years] | | | | | | | | | | | | 0.6058 |
| <65 | 435 | 6 | 1.4 | 392 | 4 | 1.0 | 0.6373 | 0.74 ( 0.21, 2.60) | 0.74 ( 0.21, 2.63) | 0.00 (-0.02, 0.01) | | |
| >=65 | 839 | 14 | 1.7 | 886 | 16 | 1.8 | 0.8275 | 1.08 ( 0.53, 2.20) | 1.08 ( 0.53, 2.23) | 0.00 (-0.01, 0.01) | | |
| Region | | | | | | | | | | | | 0.9720 |
| North America | 161 | 4 | 2.5 | 159 | 3 | 1.9 | 0.7148 | 0.76 ( 0.17, 3.34) | 0.75 ( 0.17, 3.43) | -0.01 (-0.04, 0.03) | | |
| Latin America | 420 | 6 | 1.4 | 440 | 6 | 1.4 | 0.9353 | 0.95 ( 0.31, 2.94) | 0.95 ( 0.31, 2.98) | 0.00 (-0.02, 0.02) | | |
| Europe | 469 | 8 | 1.7 | 467 | 8 | 1.7 | 0.9931 | 1.00 ( 0.38, 2.65) | 1.00 ( 0.37, 2.70) | 0.00 (-0.02, 0.02) | | |
| Asia | 174 | 1 | 0.6 | 165 | 2 | 1.2 | 0.5311 | 2.11 ( 0.19, 23.04) | 2.12 ( 0.19, 23.63) | 0.01 (-0.01, 0.03) | | |
| Other | 50 | 1 | 2.0 | 47 | 1 | 2.1 | 0.9647 | 1.06 ( 0.07, 16.53) | 1.07 ( 0.06, 17.53) | 0.00 (-0.06, 0.06) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9927 |
| Diabetic | 694 | 11 | 1.6 | 698 | 11 | 1.6 | 0.9892 | 0.99 ( 0.43, 2.28) | 0.99 ( 0.43, 2.31) | 0.00 (-0.01, 0.01) | | |
| Non-Diabetic | 580 | 9 | 1.6 | 580 | 9 | 1.6 | 1.0000 | 1.00 ( 0.40, 2.50) | 1.00 ( 0.39, 2.54) | 0.00 (-0.01, 0.01) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7147 |
| <30 | 889 | 14 | 1.6 | 836 | 12 | 1.4 | 0.8123 | 0.91 ( 0.42, 1.96) | 0.91 ( 0.42, 1.98) | 0.00 (-0.01, 0.01) | | |
| >=30 | 385 | 6 | 1.6 | 442 | 8 | 1.8 | 0.7797 | 1.16 ( 0.41, 3.32) | 1.16 ( 0.40, 3.39) | 0.00 (-0.02, 0.02) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.6101 |
| <130 | 857 | 13 | 1.5 | 834 | 11 | 1.3 | 0.7308 | 0.87 ( 0.39, 1.93) | 0.87 ( 0.39, 1.95) | 0.00 (-0.01, 0.01) | | |
| >=130 | 417 | 7 | 1.7 | 444 | 9 | 2.0 | 0.7052 | 1.21 ( 0.45, 3.21) | 1.21 ( 0.45, 3.28) | 0.00 (-0.01, 0.02) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.1369 |
| <75 | 718 | 17 | 2.4 | 678 | 13 | 1.9 | 0.5620 | 0.81 ( 0.40, 1.65) | 0.81 ( 0.39, 1.67) | 0.00 (-0.02, 0.01) | | |
| 75 to <85 | 348 | 0 | 0 | 382 | 6 | 1.6 | 0.0310 | 11.85 ( 0.67,209.51) | 12.03 ( 0.68,214.39) | 0.02 ( 0.00, 0.03) | | |
| >=85 | 208 | 3 | 1.4 | 218 | 1 | 0.5 | 0.2927 | 0.32 ( 0.03, 3.03) | 0.31 ( 0.03, 3.05) | -0.01 (-0.03, 0.01) | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.2750 |
| <30 | 89 | 2 | 2.2 | 115 | 6 | 5.2 | 0.2784 | 2.32 ( 0.48, 11.23) | 2.39 ( 0.47, 12.16) | 0.03 (-0.02, 0.08) | |
| 30 to <45 | 348 | 7 | 2.0 | 345 | 3 | 0.9 | 0.2075 | 0.43 ( 0.11, 1.66) | 0.43 ( 0.11, 1.67) | -0.01 (-0.03, 0.01) | |
| >=45 | 837 | 11 | 1.3 | 818 | 11 | 1.3 | 0.9568 | 1.02 ( 0.45, 2.35) | 1.02 ( 0.44, 2.37) | 0.00 (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.7437 |
| Normal (<30) | 452 | 5 | 1.1 | 456 | 7 | 1.5 | 0.5715 | 1.39 ( 0.44, 4.34) | 1.39 ( 0.44, 4.42) | 0.00 (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 627 | 11 | 1.8 | 608 | 11 | 1.8 | 0.9419 | 1.03 ( 0.45, 2.36) | 1.03 ( 0.44, 2.40) | 0.00 (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 189 | 3 | 1.6 | 207 | 2 | 1.0 | 0.5803 | 0.61 ( 0.10, 3.60) | 0.60 ( 0.10, 3.66) | -0.01 (-0.03, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8628 |
| Low, moderate or high | 953 | 13 | 1.4 | 947 | 13 | 1.4 | 0.9871 | 1.01 ( 0.47, 2.16) | 1.01 ( 0.46, 2.18) | 0.00 (-0.01, 0.01) | |
| Very high | 315 | 6 | 1.9 | 325 | 7 | 2.2 | 0.8233 | 1.13 ( 0.38, 3.33) | 1.13 ( 0.38, 3.41) | 0.00 (-0.02, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.0790 |
| No | 161 | 2 | 1.2 | 168 | 7 | 4.2 | 0.1040 | 3.35 ( 0.71, 15.91) | 3.46 ( 0.71, 16.89) | 0.03 (-0.01, 0.06) | |
| Yes | 1113 | 18 | 1.6 | 1110 | 13 | 1.2 | 0.3698 | 0.72 ( 0.36, 1.47) | 0.72 ( 0.35, 1.48) | 0.00 (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.2352 |
| No | 62 | 2 | 3.2 | 72 | 0 | 0 | 0.1936 | 0.17 (<0.01, 3.53) | 0.17 (<0.01, 3.54) | -0.03 (-0.08, 0.02) | |
| Yes | 1212 | 18 | 1.5 | 1206 | 20 | 1.7 | 0.7320 | 1.12 ( 0.59, 2.10) | 1.12 ( 0.59, 2.13) | 0.00 (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.4083 |
| No | 46 | 1 | 2.2 | 57 | 0 | 0 | 0.3852 | 0.27 ( 0.01, 6.48) | 0.26 ( 0.01, 6.63) | -0.02 (-0.08, 0.03) | |
| Yes | 1228 | 19 | 1.5 | 1221 | 20 | 1.6 | 0.8576 | 1.06 ( 0.57, 1.97) | 1.06 ( 0.56, 2.00) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 2 | 0.2 | 1278 | 1 | 0.1 | 0.5616 | 0.50 ( 0.05, 5.49) | 0.50 ( 0.05, 5.50) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 958 | 1 | 0.1 | 975 | 1 | 0.1 | | | | | |
| Female | 316 | 1 | 0.3 | 303 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 1 | 0.2 | 392 | 0 | 0 | | | | | |
| >=65 | 839 | 1 | 0.1 | 886 | 1 | 0.1 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 0 | 0 | | | | | |
| Latin America | 420 | 0 | 0 | 440 | 0 | 0 | | | | | |
| Europe | 469 | 1 | 0.2 | 467 | 1 | 0.2 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 0 | 0 | 698 | 1 | 0.1 | | | | | |
| Non-Diabetic | 580 | 2 | 0.3 | 580 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 2 | 0.2 | 836 | 1 | 0.1 | | | | | |
| >=30 | 385 | 0 | 0 | 442 | 0 | 0 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 1 | 0.1 | 834 | 0 | 0 | | | | | |
| >=130 | 417 | 1 | 0.2 | 444 | 1 | 0.2 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 1 | 0.1 | 678 | 0 | 0 | | | | | |
| 75 to <85 | 348 | 0 | 0 | 382 | 1 | 0.3 | | | | | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 0 | 0 | | | | | |
| 30 to <45 | 348 | 0 | 0 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 2 | 0.2 | 818 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 0 | 0 | 456 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 1 | 0.2 | 608 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 2 | 0.2 | 947 | 1 | 0.1 | | | | | |
| Very high | 315 | 0 | 0 | 325 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 0 | 0 | 168 | 0 | 0 | | | | | |
| Yes | 1113 | 2 | 0.2 | 1110 | 1 | 0.1 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 1 | 0.1 | 1206 | 1 | 0.1 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 0 | 0 | | | | | |
| Yes | 1228 | 2 | 0.2 | 1221 | 1 | 0.1 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 6 | 0.5 | 1278 | 6 | 0.5 | 0.9957 | 1.00 ( 0.32, 3.08) | 1.00 ( 0.32, 3.10) | 0.00 (-0.01, 0.01) | |
| Sex | | | | | | | | | | | |
| Male | 958 | 5 | 0.5 | 975 | 1 | 0.1 | | | | | |
| Female | 316 | 1 | 0.3 | 303 | 5 | 1.7 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 2 | 0.5 | 392 | 1 | 0.3 | | | | | |
| >=65 | 839 | 4 | 0.5 | 886 | 5 | 0.6 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 1 | 0.6 | | | | | |
| Latin America | 420 | 2 | 0.5 | 440 | 2 | 0.5 | | | | | |
| Europe | 469 | 2 | 0.4 | 467 | 3 | 0.6 | | | | | |
| Asia | 174 | 1 | 0.6 | 165 | 0 | 0 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 5 | 0.7 | 698 | 2 | 0.3 | | | | | |
| Non-Diabetic | 580 | 1 | 0.2 | 580 | 4 | 0.7 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 3 | 0.3 | 836 | 4 | 0.5 | | | | | |
| >=30 | 385 | 3 | 0.8 | 442 | 2 | 0.5 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 3 | 0.4 | 834 | 3 | 0.4 | | | | | |
| >=130 | 417 | 3 | 0.7 | 444 | 3 | 0.7 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 5 | 0.7 | 678 | 4 | 0.6 | | | | | |
| 75 to <85 | 348 | 0 | 0 | 382 | 2 | 0.5 | | | | | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 2 | 1.7 | | | | | |
| 30 to <45 | 348 | 3 | 0.9 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 3 | 0.4 | 818 | 4 | 0.5 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 1 | 0.2 | 456 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 3 | 0.5 | 608 | 5 | 0.8 | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 2 | 0.2 | 947 | 4 | 0.4 | | | | | |
| Very high | 315 | 3 | 1.0 | 325 | 2 | 0.6 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.4769 |
| No | 161 | 0 | 0 | 168 | 1 | 0.6 | 0.4969 | 2.88 ( 0.12, 70.08) | 2.89 ( 0.12, 71.52) | 0.01 (-0.01, 0.02) | |
| Yes | 1113 | 6 | 0.5 | 1110 | 5 | 0.5 | 0.7659 | 0.84 ( 0.26, 2.73) | 0.83 ( 0.25, 2.74) | 0.00 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.4081 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 ( 0.01, 6.94) | 0.28 ( 0.01, 7.07) | -0.02 (-0.06, 0.03) | |
| Yes | 1212 | 5 | 0.4 | 1206 | 6 | 0.5 | 0.7562 | 1.21 ( 0.37, 3.94) | 1.21 ( 0.37, 3.97) | 0.00 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.3869 |
| No | 46 | 1 | 2.2 | 57 | 0 | 0 | 0.3852 | 0.27 ( 0.01, 6.48) | 0.26 ( 0.01, 6.63) | -0.02 (-0.08, 0.03) | |
| Yes | 1228 | 5 | 0.4 | 1221 | 6 | 0.5 | 0.7553 | 1.21 ( 0.37, 3.94) | 1.21 ( 0.37, 3.97) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 20 | 1.6 | 1278 | 22 | 1.7 | 0.7635 | 1.10 ( 0.60, 2.00) | 1.10 ( 0.60, 2.02) | 0.00 (-0.01, 0.01) | |
| Sex | | | | | | | | | | | 0.1439 |
| Male | 958 | 12 | 1.3 | 975 | 18 | 1.8 | 0.2912 | 1.47 ( 0.71, 3.04) | 1.48 ( 0.71, 3.10) | 0.01 (-0.01, 0.02) | |
| Female | 316 | 8 | 2.5 | 303 | 4 | 1.3 | 0.2745 | 0.52 ( 0.16, 1.71) | 0.52 ( 0.15, 1.73) | -0.01 (-0.03, 0.01) | |
| Age [years] | | | | | | | | | | | 0.2453 |
| <65 | 435 | 5 | 1.1 | 392 | 2 | 0.5 | 0.3164 | 0.44 ( 0.09, 2.27) | 0.44 ( 0.09, 2.29) | -0.01 (-0.02, 0.01) | |
| >=65 | 839 | 15 | 1.8 | 886 | 20 | 2.3 | 0.4894 | 1.26 ( 0.65, 2.45) | 1.27 ( 0.65, 2.49) | 0.00 (-0.01, 0.02) | |
| Region | | | | | | | | | | | 0.7723 |
| North America | 161 | 4 | 2.5 | 159 | 4 | 2.5 | 0.9857 | 1.01 ( 0.26, 3.98) | 1.01 ( 0.25, 4.12) | 0.00 (-0.03, 0.03) | |
| Latin America | 420 | 5 | 1.2 | 440 | 4 | 0.9 | 0.6852 | 0.76 ( 0.21, 2.82) | 0.76 ( 0.20, 2.86) | 0.00 (-0.02, 0.01) | |
| Europe | 469 | 10 | 2.1 | 467 | 10 | 2.1 | 0.9923 | 1.00 ( 0.42, 2.39) | 1.00 ( 0.41, 2.44) | 0.00 (-0.02, 0.02) | |
| Asia | 174 | 1 | 0.6 | 165 | 4 | 2.4 | 0.1580 | 4.22 ( 0.48, 37.35) | 4.30 ( 0.48, 38.86) | 0.02 (-0.01, 0.04) | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 ( 0.02, 52.49) | 1.06 ( 0.02, 54.66) | 0.00 (-0.04, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.0643 |
| Diabetic | 694 | 13 | 1.9 | 698 | 8 | 1.1 | 0.2658 | 0.61 ( 0.26, 1.47) | 0.61 ( 0.25, 1.47) | -0.01 (-0.02, 0.01) | |
| Non-Diabetic | 580 | 7 | 1.2 | 580 | 14 | 2.4 | 0.1232 | 2.00 ( 0.81, 4.92) | 2.02 ( 0.81, 5.05) | 0.01 ( 0.00, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.6980 |
| <30 | 889 | 17 | 1.9 | 836 | 17 | 2.0 | 0.8563 | 1.06 ( 0.55, 2.07) | 1.06 ( 0.54, 2.10) | 0.00 (-0.01, 0.01) | |
| >=30 | 385 | 3 | 0.8 | 442 | 5 | 1.1 | 0.6059 | 1.45 ( 0.35, 6.04) | 1.46 ( 0.35, 6.14) | 0.00 (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.7988 |
| <130 | 857 | 13 | 1.5 | 834 | 13 | 1.6 | 0.9443 | 1.03 ( 0.48, 2.20) | 1.03 ( 0.47, 2.23) | 0.00 (-0.01, 0.01) | |
| >=130 | 417 | 7 | 1.7 | 444 | 9 | 2.0 | 0.7052 | 1.21 ( 0.45, 3.21) | 1.21 ( 0.45, 3.28) | 0.00 (-0.01, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.4963 |
| <75 | 718 | 15 | 2.1 | 678 | 14 | 2.1 | 0.9747 | 0.99 ( 0.48, 2.03) | 0.99 ( 0.47, 2.06) | 0.00 (-0.02, 0.01) | |
| 75 to <85 | 348 | 4 | 1.1 | 382 | 4 | 1.0 | 0.8945 | 0.91 ( 0.23, 3.61) | 0.91 ( 0.23, 3.67) | 0.00 (-0.02, 0.01) | |
| >=85 | 208 | 1 | 0.5 | 218 | 4 | 1.8 | 0.1946 | 3.82 ( 0.43, 33.87) | 3.87 ( 0.43, 34.91) | 0.01 (-0.01, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.6825 |
| <30 | 89 | 1 | 1.1 | 115 | 2 | 1.7 | 0.7172 | 1.55 ( 0.14, 16.80) | 1.56 ( 0.14, 17.46) | 0.01 (-0.03, 0.04) | |
| 30 to <45 | 348 | 7 | 2.0 | 345 | 5 | 1.4 | 0.5705 | 0.72 ( 0.23, 2.25) | 0.72 ( 0.23, 2.28) | -0.01 (-0.03, 0.01) | |
| >=45 | 837 | 12 | 1.4 | 818 | 15 | 1.8 | 0.5207 | 1.28 ( 0.60, 2.72) | 1.28 ( 0.60, 2.76) | 0.00 (-0.01, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.3824 |
| Normal (<30) | 452 | 8 | 1.8 | 456 | 6 | 1.3 | 0.5787 | 0.74 ( 0.26, 2.13) | 0.74 ( 0.25, 2.15) | 0.00 (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 7 | 1.1 | 608 | 12 | 2.0 | 0.2211 | 1.77 ( 0.70, 4.46) | 1.78 ( 0.70, 4.56) | 0.01 (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 189 | 5 | 2.6 | 207 | 4 | 1.9 | 0.6343 | 0.73 ( 0.20, 2.68) | 0.73 ( 0.19, 2.74) | -0.01 (-0.04, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.6621 |
| Low, moderate or high | 953 | 15 | 1.6 | 947 | 15 | 1.6 | 0.9861 | 1.01 ( 0.49, 2.05) | 1.01 ( 0.49, 2.07) | 0.00 (-0.01, 0.01) | |
| Very high | 315 | 5 | 1.6 | 325 | 7 | 2.2 | 0.5973 | 1.36 ( 0.44, 4.23) | 1.36 ( 0.43, 4.35) | 0.01 (-0.02, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.1822 |
| No | 161 | 2 | 1.2 | 168 | 6 | 3.6 | 0.1703 | 2.88 ( 0.59, 14.04) | 2.94 ( 0.59, 14.81) | 0.02 (-0.01, 0.06) | |
| Yes | 1113 | 18 | 1.6 | 1110 | 16 | 1.4 | 0.7356 | 0.89 ( 0.46, 1.74) | 0.89 ( 0.45, 1.75) | 0.00 (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.4261 |
| No | 62 | 1 | 1.6 | 72 | 3 | 4.2 | 0.3864 | 2.58 ( 0.28, 24.21) | 2.65 ( 0.27, 26.17) | 0.03 (-0.03, 0.08) | |
| Yes | 1212 | 19 | 1.6 | 1206 | 19 | 1.6 | 0.9877 | 1.00 ( 0.53, 1.89) | 1.01 ( 0.53, 1.91) | 0.00 (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.8771 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 ( 0.02, 40.07) | 0.81 ( 0.02, 41.54) | 0.00 (-0.04, 0.04) | |
| Yes | 1228 | 20 | 1.6 | 1221 | 22 | 1.8 | 0.7414 | 1.11 ( 0.61, 2.02) | 1.11 ( 0.60, 2.04) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 6 | 0.5 | 1278 | 8 | 0.6 | 0.5960 | 1.33 ( 0.46, 3.82) | 1.33 ( 0.46, 3.85) | 0.00 ( 0.00, 0.01) | | |
| Sex | | | | | | | | | | | | 0.1775 |
| Male | 958 | 4 | 0.4 | 975 | 8 | 0.8 | 0.2594 | 1.97 ( 0.59, 6.50) | 1.97 ( 0.59, 6.57) | 0.00 ( 0.00, 0.01) | | |
| Female | 316 | 2 | 0.6 | 303 | 0 | 0 | 0.2621 | 0.21 ( 0.01, 4.33) | 0.21 (<0.01, 4.33) | -0.01 (-0.02, 0.00) | | |
| Age [years] | | | | | | | | | | | | 0.8353 |
| <65 | 435 | 2 | 0.5 | 392 | 2 | 0.5 | 0.9169 | 1.11 ( 0.16, 7.84) | 1.11 ( 0.16, 7.92) | 0.00 (-0.01, 0.01) | | |
| >=65 | 839 | 4 | 0.5 | 886 | 6 | 0.7 | 0.5836 | 1.42 ( 0.40, 5.02) | 1.42 ( 0.40, 5.06) | 0.00 (-0.01, 0.01) | | |
| Region | | | | | | | | | | | | |
| North America | 161 | 2 | 1.2 | 159 | 2 | 1.3 | | | | | | |
| Latin America | 420 | 0 | 0 | 440 | 1 | 0.2 | | | | | | |
| Europe | 469 | 4 | 0.9 | 467 | 4 | 0.9 | | | | | | |
| Asia | 174 | 0 | 0 | 165 | 1 | 0.6 | | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3639 |
| Diabetic | 694 | 4 | 0.6 | 698 | 7 | 1.0 | 0.3689 | 1.74 ( 0.51, 5.92) | 1.75 ( 0.51, 6.00) | 0.00 (-0.01, 0.01) | | |
| Non-Diabetic | 580 | 2 | 0.3 | 580 | 1 | 0.2 | 0.5632 | 0.50 ( 0.05, 5.50) | 0.50 ( 0.05, 5.52) | 0.00 (-0.01, 0.00) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7258 |
| <30 | 889 | 5 | 0.6 | 836 | 7 | 0.8 | 0.4924 | 1.49 ( 0.47, 4.67) | 1.49 ( 0.47, 4.72) | 0.00 (-0.01, 0.01) | | |
| >=30 | 385 | 1 | 0.3 | 442 | 1 | 0.2 | 0.9221 | 0.87 ( 0.05, 13.88) | 0.87 ( 0.05, 13.97) | 0.00 (-0.01, 0.01) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 857 | 5 | 0.6 | 834 | 4 | 0.5 | | | | | | |
| >=130 | 417 | 1 | 0.2 | 444 | 4 | 0.9 | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 718 | 3 | 0.4 | 678 | 6 | 0.9 | | | | | | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 2 | 0.5 | | | | | | |
| >=85 | 208 | 2 | 1.0 | 218 | 0 | 0 | | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.5270 |
| <30 | 89 | 1 | 1.1 | 115 | 0 | 0 | 0.3697 | 0.26 ( 0.01, 6.27) | 0.26 ( 0.01, 6.35) | -0.01 (-0.04, 0.02) | |
| 30 to <45 | 348 | 0 | 0 | 345 | 1 | 0.3 | 0.4751 | 3.03 ( 0.12, 74.02) | 3.03 ( 0.12, 74.76) | 0.00 (-0.01, 0.01) | |
| >=45 | 837 | 5 | 0.6 | 818 | 7 | 0.9 | 0.5356 | 1.43 ( 0.46, 4.50) | 1.44 ( 0.45, 4.54) | 0.00 (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 0 | 0 | 456 | 2 | 0.4 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 4 | 0.6 | 608 | 4 | 0.7 | | | | | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 207 | 2 | 1.0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.7285 |
| Low, moderate or high | 953 | 5 | 0.5 | 947 | 6 | 0.6 | 0.7544 | 1.21 ( 0.37, 3.94) | 1.21 ( 0.37, 3.97) | 0.00 (-0.01, 0.01) | |
| Very high | 315 | 1 | 0.3 | 325 | 2 | 0.6 | 0.5812 | 1.94 ( 0.18, 21.27) | 1.94 ( 0.18, 21.55) | 0.00 (-0.01, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3428 |
| No | 161 | 0 | 0 | 168 | 2 | 1.2 | 0.2613 | 4.79 ( 0.23, 99.07) | 4.85 ( 0.23,101.80) | 0.01 (-0.01, 0.03) | |
| Yes | 1113 | 6 | 0.5 | 1110 | 6 | 0.5 | 0.9963 | 1.00 ( 0.32, 3.10) | 1.00 ( 0.32, 3.12) | 0.00 (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.3172 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 ( 0.01, 6.94) | 0.28 ( 0.01, 7.07) | -0.02 (-0.06, 0.03) | |
| Yes | 1212 | 5 | 0.4 | 1206 | 8 | 0.7 | 0.3991 | 1.61 ( 0.53, 4.90) | 1.61 ( 0.53, 4.94) | 0.00 ( 0.00, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.6707 |
| No | 46 | 0 | 0 | 57 | 1 | 1.8 | 0.5704 | 2.43 ( 0.10, 58.31) | 2.47 ( 0.10, 62.05) | 0.02 (-0.04, 0.07) | |
| Yes | 1228 | 6 | 0.5 | 1221 | 7 | 0.6 | 0.7730 | 1.17 ( 0.40, 3.48) | 1.17 ( 0.39, 3.50) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 33 | 2.6 | 1278 | 38 | 3.0 | 0.5562 | 1.15 ( 0.72, 1.82) | 1.15 ( 0.72, 1.85) | 0.00 (-0.01, 0.02) | |
| Sex | | | | | | | | | | | 0.2115 |
| Male | 958 | 28 | 2.9 | 975 | 28 | 2.9 | 0.9467 | 0.98 ( 0.59, 1.65) | 0.98 ( 0.58, 1.67) | 0.00 (-0.02, 0.01) | |
| Female | 316 | 5 | 1.6 | 303 | 10 | 3.3 | 0.1647 | 2.09 ( 0.72, 6.03) | 2.12 ( 0.72, 6.28) | 0.02 (-0.01, 0.04) | |
| Age [years] | | | | | | | | | | | 0.3807 |
| <65 | 435 | 11 | 2.5 | 392 | 8 | 2.0 | 0.6400 | 0.81 ( 0.33, 1.99) | 0.80 ( 0.32, 2.02) | 0.00 (-0.03, 0.02) | |
| >=65 | 839 | 22 | 2.6 | 886 | 30 | 3.4 | 0.3537 | 1.29 ( 0.75, 2.22) | 1.30 ( 0.74, 2.27) | 0.01 (-0.01, 0.02) | |
| Region | | | | | | | | | | | 0.7645 |
| North America | 161 | 12 | 7.5 | 159 | 12 | 7.5 | 0.9746 | 1.01 ( 0.47, 2.19) | 1.01 ( 0.44, 2.33) | 0.00 (-0.06, 0.06) | |
| Latin America | 420 | 8 | 1.9 | 440 | 11 | 2.5 | 0.5528 | 1.31 ( 0.53, 3.23) | 1.32 ( 0.53, 3.32) | 0.01 (-0.01, 0.03) | |
| Europe | 469 | 7 | 1.5 | 467 | 11 | 2.4 | 0.3365 | 1.58 ( 0.62, 4.04) | 1.59 ( 0.61, 4.14) | 0.01 (-0.01, 0.03) | |
| Asia | 174 | 4 | 2.3 | 165 | 4 | 2.4 | 0.9394 | 1.05 ( 0.27, 4.15) | 1.06 ( 0.26, 4.29) | 0.00 (-0.03, 0.03) | |
| Other | 50 | 2 | 4.0 | 47 | 0 | 0 | 0.2628 | 0.21 ( 0.01, 4.31) | 0.20 (<0.01, 4.37) | -0.04 (-0.10, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.6556 |
| Diabetic | 694 | 20 | 2.9 | 698 | 25 | 3.6 | 0.4604 | 1.24 ( 0.70, 2.22) | 1.25 ( 0.69, 2.28) | 0.01 (-0.01, 0.03) | |
| Non-Diabetic | 580 | 13 | 2.2 | 580 | 13 | 2.2 | 1.0000 | 1.00 ( 0.47, 2.14) | 1.00 ( 0.46, 2.18) | 0.00 (-0.02, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.5492 |
| <30 | 889 | 21 | 2.4 | 836 | 25 | 3.0 | 0.4183 | 1.27 ( 0.71, 2.24) | 1.27 ( 0.71, 2.29) | 0.01 (-0.01, 0.02) | |
| >=30 | 385 | 12 | 3.1 | 442 | 13 | 2.9 | 0.8830 | 0.94 ( 0.44, 2.04) | 0.94 ( 0.42, 2.09) | 0.00 (-0.03, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.0323 |
| <130 | 857 | 22 | 2.6 | 834 | 33 | 4.0 | 0.1073 | 1.54 ( 0.91, 2.62) | 1.56 ( 0.90, 2.71) | 0.01 ( 0.00, 0.03) | |
| >=130 | 417 | 11 | 2.6 | 444 | 5 | 1.1 | 0.1007 | 0.43 ( 0.15, 1.22) | 0.42 ( 0.14, 1.22) | -0.02 (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.8043 |
| <75 | 718 | 21 | 2.9 | 678 | 25 | 3.7 | 0.4251 | 1.26 ( 0.71, 2.23) | 1.27 ( 0.70, 2.29) | 0.01 (-0.01, 0.03) | |
| 75 to <85 | 348 | 10 | 2.9 | 382 | 10 | 2.6 | 0.8325 | 0.91 ( 0.38, 2.16) | 0.91 ( 0.37, 2.21) | 0.00 (-0.03, 0.02) | |
| >=85 | 208 | 2 | 1.0 | 218 | 3 | 1.4 | 0.6912 | 1.43 ( 0.24, 8.48) | 1.44 ( 0.24, 8.69) | 0.00 (-0.02, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0802 |
| <30 | 89 | 2 | 2.2 | 115 | 10 | 8.7 | 0.0522 | 3.87 ( 0.87, 17.22) | 4.14 ( 0.88, 19.41) | 0.06 ( 0.00, 0.12) | |
| 30 to <45 | 348 | 8 | 2.3 | 345 | 12 | 3.5 | 0.3538 | 1.51 ( 0.63, 3.66) | 1.53 ( 0.62, 3.79) | 0.01 (-0.01, 0.04) | |
| >=45 | 837 | 23 | 2.7 | 818 | 16 | 2.0 | 0.2883 | 0.71 ( 0.38, 1.34) | 0.71 ( 0.37, 1.35) | -0.01 (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.2474 |
| Normal (<30) | 452 | 9 | 2.0 | 456 | 12 | 2.6 | 0.5209 | 1.32 ( 0.56, 3.11) | 1.33 ( 0.55, 3.19) | 0.01 (-0.01, 0.03) | |
| Microalbuminuria (30 to <=300) | 627 | 15 | 2.4 | 608 | 21 | 3.5 | 0.2676 | 1.44 ( 0.75, 2.77) | 1.46 ( 0.75, 2.86) | 0.01 (-0.01, 0.03) | |
| Macroalbuminuria (>300) | 189 | 9 | 4.8 | 207 | 5 | 2.4 | 0.2066 | 0.51 ( 0.17, 1.49) | 0.50 ( 0.16, 1.50) | -0.02 (-0.06, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0131 |
| Low, moderate or high | 953 | 27 | 2.8 | 947 | 20 | 2.1 | 0.3115 | 0.75 ( 0.42, 1.32) | 0.74 ( 0.41, 1.33) | -0.01 (-0.02, 0.01) | |
| Very high | 315 | 6 | 1.9 | 325 | 18 | 5.5 | 0.0156 | 2.91 ( 1.17, 7.23) | 3.02 ( 1.18, 7.71) | 0.04 ( 0.01, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3485 |
| No | 161 | 4 | 2.5 | 168 | 8 | 4.8 | 0.2707 | 1.92 ( 0.59, 6.24) | 1.96 ( 0.58, 6.65) | 0.02 (-0.02, 0.06) | |
| Yes | 1113 | 29 | 2.6 | 1110 | 30 | 2.7 | 0.8867 | 1.04 ( 0.63, 1.72) | 1.04 ( 0.62, 1.74) | 0.00 (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.2285 |
| No | 62 | 4 | 6.5 | 72 | 2 | 2.8 | 0.3052 | 0.43 ( 0.08, 2.27) | 0.41 ( 0.07, 2.34) | -0.04 (-0.11, 0.04) | |
| Yes | 1212 | 29 | 2.4 | 1206 | 36 | 3.0 | 0.3679 | 1.25 ( 0.77, 2.02) | 1.26 ( 0.76, 2.06) | 0.01 (-0.01, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.8586 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 ( 0.02, 40.07) | 0.81 ( 0.02, 41.54) | 0.00 (-0.04, 0.04) | |
| Yes | 1228 | 33 | 2.7 | 1221 | 38 | 3.1 | 0.5309 | 1.16 ( 0.73, 1.83) | 1.16 ( 0.72, 1.87) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 29 | 2.3 | 1278 | 31 | 2.4 | 0.8034 | 1.07 ( 0.65, 1.76) | 1.07 ( 0.64, 1.78) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | 0.3336 |
| Male | 958 | 25 | 2.6 | 975 | 24 | 2.5 | 0.8360 | 0.94 ( 0.54, 1.64) | 0.94 ( 0.53, 1.66) | 0.00 | (-0.02, 0.01) | |
| Female | 316 | 4 | 1.3 | 303 | 7 | 2.3 | 0.3255 | 1.83 ( 0.54, 6.17) | 1.84 ( 0.53, 6.37) | 0.01 | (-0.01, 0.03) | |
| Age [years] | | | | | | | | | | | | 0.4523 |
| <65 | 435 | 10 | 2.3 | 392 | 7 | 1.8 | 0.6036 | 0.78 ( 0.30, 2.02) | 0.77 ( 0.29, 2.05) | -0.01 | (-0.02, 0.01) | |
| >=65 | 839 | 19 | 2.3 | 886 | 24 | 2.7 | 0.5542 | 1.20 ( 0.66, 2.17) | 1.20 ( 0.65, 2.21) | 0.00 | (-0.01, 0.02) | |
| Region | | | | | | | | | | | | 0.9732 |
| North America | 161 | 11 | 6.8 | 159 | 10 | 6.3 | 0.8445 | 0.92 ( 0.40, 2.11) | 0.92 ( 0.38, 2.22) | -0.01 | (-0.06, 0.05) | |
| Latin America | 420 | 7 | 1.7 | 440 | 9 | 2.0 | 0.6811 | 1.23 ( 0.46, 3.27) | 1.23 ( 0.45, 3.34) | 0.00 | (-0.01, 0.02) | |
| Europe | 469 | 7 | 1.5 | 467 | 9 | 1.9 | 0.6080 | 1.29 ( 0.48, 3.44) | 1.30 ( 0.48, 3.51) | 0.00 | (-0.01, 0.02) | |
| Asia | 174 | 4 | 2.3 | 165 | 3 | 1.8 | 0.7558 | 0.79 ( 0.18, 3.48) | 0.79 ( 0.17, 3.57) | 0.00 | (-0.03, 0.03) | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 ( 0.02, 52.49) | 1.06 ( 0.02, 54.66) | 0.00 | (-0.04, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.8510 |
| Diabetic | 694 | 18 | 2.6 | 698 | 20 | 2.9 | 0.7558 | 1.10 ( 0.59, 2.07) | 1.11 ( 0.58, 2.11) | 0.00 | (-0.01, 0.02) | |
| Non-Diabetic | 580 | 11 | 1.9 | 580 | 11 | 1.9 | 1.0000 | 1.00 ( 0.44, 2.29) | 1.00 ( 0.43, 2.33) | 0.00 | (-0.02, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5800 |
| <30 | 889 | 19 | 2.1 | 836 | 21 | 2.5 | 0.6053 | 1.18 ( 0.64, 2.17) | 1.18 ( 0.63, 2.21) | 0.00 | (-0.01, 0.02) | |
| >=30 | 385 | 10 | 2.6 | 442 | 10 | 2.3 | 0.7545 | 0.87 ( 0.37, 2.07) | 0.87 ( 0.36, 2.11) | 0.00 | (-0.02, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0390 |
| <130 | 857 | 19 | 2.2 | 834 | 27 | 3.2 | 0.1972 | 1.46 ( 0.82, 2.61) | 1.48 ( 0.81, 2.67) | 0.01 | (-0.01, 0.03) | |
| >=130 | 417 | 10 | 2.4 | 444 | 4 | 0.9 | 0.0826 | 0.38 ( 0.12, 1.19) | 0.37 ( 0.12, 1.19) | -0.01 | (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7684 |
| <75 | 718 | 18 | 2.5 | 678 | 20 | 2.9 | 0.6113 | 1.18 ( 0.63, 2.21) | 1.18 ( 0.62, 2.25) | 0.00 | (-0.01, 0.02) | |
| 75 to <85 | 348 | 9 | 2.6 | 382 | 8 | 2.1 | 0.6598 | 0.81 ( 0.32, 2.08) | 0.81 ( 0.31, 2.11) | 0.00 | (-0.03, 0.02) | |
| >=85 | 208 | 2 | 1.0 | 218 | 3 | 1.4 | 0.6912 | 1.43 ( 0.24, 8.48) | 1.44 ( 0.24, 8.69) | 0.00 | (-0.02, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.1117 |
| <30 | 89 | 1 | 1.1 | 115 | 7 | 6.1 | 0.0701 | 5.42 ( 0.68, 43.23) | 5.70 ( 0.69, 47.24) | 0.05 ( 0.00, 0.10) | |
| 30 to <45 | 348 | 8 | 2.3 | 345 | 11 | 3.2 | 0.4734 | 1.39 ( 0.56, 3.41) | 1.40 ( 0.56, 3.52) | 0.01 (-0.02, 0.03) | |
| >=45 | 837 | 20 | 2.4 | 818 | 13 | 1.6 | 0.2443 | 0.67 ( 0.33, 1.33) | 0.66 ( 0.33, 1.34) | -0.01 (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.4467 |
| Normal (<30) | 452 | 8 | 1.8 | 456 | 11 | 2.4 | 0.4989 | 1.36 ( 0.55, 3.36) | 1.37 ( 0.55, 3.44) | 0.01 (-0.01, 0.03) | |
| Microalbuminuria (30 to <=300) | 627 | 13 | 2.1 | 608 | 15 | 2.5 | 0.6421 | 1.19 ( 0.57, 2.48) | 1.19 ( 0.56, 2.53) | 0.00 (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 189 | 8 | 4.2 | 207 | 5 | 2.4 | 0.3107 | 0.57 ( 0.19, 1.71) | 0.56 ( 0.18, 1.74) | -0.02 (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0266 |
| Low, moderate or high | 953 | 24 | 2.5 | 947 | 17 | 1.8 | 0.2780 | 0.71 ( 0.39, 1.32) | 0.71 ( 0.38, 1.33) | -0.01 (-0.02, 0.01) | |
| Very high | 315 | 5 | 1.6 | 325 | 14 | 4.3 | 0.0426 | 2.71 ( 0.99, 7.45) | 2.79 ( 0.99, 7.84) | 0.03 ( 0.00, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.0710 |
| No | 161 | 2 | 1.2 | 168 | 8 | 4.8 | 0.0630 | 3.83 ( 0.83, 17.78) | 3.98 ( 0.83, 19.01) | 0.04 ( 0.00, 0.07) | |
| Yes | 1113 | 27 | 2.4 | 1110 | 23 | 2.1 | 0.5738 | 0.85 ( 0.49, 1.48) | 0.85 ( 0.48, 1.49) | 0.00 (-0.02, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.2633 |
| No | 62 | 4 | 6.5 | 72 | 2 | 2.8 | 0.3052 | 0.43 ( 0.08, 2.27) | 0.41 ( 0.07, 2.34) | -0.04 (-0.11, 0.04) | |
| Yes | 1212 | 25 | 2.1 | 1206 | 29 | 2.4 | 0.5694 | 1.17 ( 0.69, 1.98) | 1.17 ( 0.68, 2.01) | 0.00 (-0.01, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.8880 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 ( 0.02, 40.07) | 0.81 ( 0.02, 41.54) | 0.00 (-0.04, 0.04) | |
| Yes | 1228 | 29 | 2.4 | 1221 | 31 | 2.5 | 0.7765 | 1.08 ( 0.65, 1.77) | 1.08 ( 0.65, 1.80) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 95 | 7.5 | 1278 | 63 | 4.9 | 0.0081 | 0.66 | ( 0.49, 0.90) | 0.64 | ( 0.46, 0.89) | -0.03 | (-0.04,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.9868 |
| Male | 958 | 73 | 7.6 | 975 | 49 | 5.0 | 0.0190 | 0.66 | ( 0.46, 0.94) | 0.64 | ( 0.44, 0.93) | -0.03 | (-0.05, 0.00) | |
| Female | 316 | 22 | 7.0 | 303 | 14 | 4.6 | 0.2134 | 0.66 | ( 0.35, 1.27) | 0.65 | ( 0.32, 1.29) | -0.02 | (-0.06, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6357 |
| <65 | 435 | 37 | 8.5 | 392 | 20 | 5.1 | 0.0537 | 0.60 | ( 0.35, 1.02) | 0.58 | ( 0.33, 1.01) | -0.03 | (-0.07, 0.00) | |
| >=65 | 839 | 58 | 6.9 | 886 | 43 | 4.9 | 0.0686 | 0.70 | ( 0.48, 1.03) | 0.69 | ( 0.46, 1.03) | -0.02 | (-0.04, 0.00) | |
| Region | | | | | | | | | | | | | | 0.4158 |
| North America | 161 | 21 | 13.0 | 159 | 20 | 12.6 | 0.9010 | 0.96 | ( 0.54, 1.71) | 0.96 | ( 0.50, 1.85) | 0.00 | (-0.08, 0.07) | |
| Latin America | 420 | 36 | 8.6 | 440 | 19 | 4.3 | 0.0108 | 0.50 | ( 0.29, 0.86) | 0.48 | ( 0.27, 0.85) | -0.04 | (-0.08,-0.01) | |
| Europe | 469 | 32 | 6.8 | 467 | 21 | 4.5 | 0.1236 | 0.66 | ( 0.39, 1.13) | 0.64 | ( 0.37, 1.13) | -0.02 | (-0.05, 0.01) | |
| Asia | 174 | 3 | 1.7 | 165 | 3 | 1.8 | 0.9477 | 1.05 | ( 0.22, 5.15) | 1.06 | ( 0.21, 5.31) | 0.00 | (-0.03, 0.03) | |
| Other | 50 | 3 | 6.0 | 47 | 0 | 0 | 0.1415 | 0.15 | (<0.01, 2.86) | 0.14 | (<0.01, 2.84) | -0.06 | (-0.13, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.1531 |
| Diabetic | 694 | 48 | 6.9 | 698 | 39 | 5.6 | 0.3057 | 0.81 | ( 0.54, 1.22) | 0.80 | ( 0.51, 1.23) | -0.01 | (-0.04, 0.01) | |
| Non-Diabetic | 580 | 47 | 8.1 | 580 | 24 | 4.1 | 0.0048 | 0.51 | ( 0.32, 0.82) | 0.49 | ( 0.30, 0.81) | -0.04 | (-0.07,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9568 |
| <30 | 889 | 57 | 6.4 | 836 | 35 | 4.2 | 0.0398 | 0.65 | ( 0.43, 0.98) | 0.64 | ( 0.41, 0.98) | -0.02 | (-0.04, 0.00) | |
| >=30 | 385 | 38 | 9.9 | 442 | 28 | 6.3 | 0.0613 | 0.64 | ( 0.40, 1.03) | 0.62 | ( 0.37, 1.03) | -0.04 | (-0.07, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2363 |
| <130 | 857 | 73 | 8.5 | 834 | 42 | 5.0 | 0.0045 | 0.59 | ( 0.41, 0.85) | 0.57 | ( 0.38, 0.84) | -0.03 | (-0.06,-0.01) | |
| >=130 | 417 | 22 | 5.3 | 444 | 21 | 4.7 | 0.7132 | 0.90 | ( 0.50, 1.61) | 0.89 | ( 0.48, 1.65) | -0.01 | (-0.03, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7826 |
| <75 | 718 | 67 | 9.3 | 678 | 41 | 6.0 | 0.0217 | 0.65 | ( 0.45, 0.94) | 0.63 | ( 0.42, 0.94) | -0.03 | (-0.06,-0.01) | |
| 75 to <85 | 348 | 21 | 6.0 | 382 | 15 | 3.9 | 0.1890 | 0.65 | ( 0.34, 1.24) | 0.64 | ( 0.32, 1.26) | -0.02 | (-0.05, 0.01) | |
| >=85 | 208 | 7 | 3.4 | 218 | 7 | 3.2 | 0.9288 | 0.95 | ( 0.34, 2.67) | 0.95 | ( 0.33, 2.76) | 0.00 | (-0.04, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1619 |
| <30 | 89 | 11 | 12.4 | 115 | 16 | 13.9 | 0.7454 | 1.13 ( 0.55, 2.30) | 1.15 ( 0.50, 2.61) | 0.02 | (-0.08, 0.11) | |
| 30 to <45 | 348 | 35 | 10.1 | 345 | 16 | 4.6 | 0.0063 | 0.46 ( 0.26, 0.82) | 0.43 ( 0.24, 0.80) | -0.05 | (-0.09,-0.02) | |
| >=45 | 837 | 49 | 5.9 | 818 | 31 | 3.8 | 0.0503 | 0.65 ( 0.42, >1.00) | 0.63 ( 0.40, 1.00) | -0.02 | (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0101 |
| Normal (<30) | 452 | 34 | 7.5 | 456 | 20 | 4.4 | 0.0457 | 0.58 ( 0.34, <1.00) | 0.56 ( 0.32, 1.00) | -0.03 | (-0.06, 0.00) | |
| Microalbuminuria (30 to <=300) | 627 | 49 | 7.8 | 608 | 23 | 3.8 | 0.0025 | 0.48 ( 0.30, 0.78) | 0.46 ( 0.28, 0.77) | -0.04 | (-0.07,-0.01) | |
| Macroalbuminuria (>300) | 189 | 10 | 5.3 | 207 | 20 | 9.7 | 0.1006 | 1.83 ( 0.88, 3.80) | 1.91 ( 0.87, 4.20) | 0.04 | (-0.01, 0.10) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.1626 |
| Low, moderate or high | 953 | 61 | 6.4 | 947 | 34 | 3.6 | 0.0049 | 0.56 ( 0.37, 0.84) | 0.54 ( 0.35, 0.84) | -0.03 | (-0.05,-0.01) | |
| Very high | 315 | 32 | 10.2 | 325 | 29 | 8.9 | 0.5946 | 0.88 ( 0.54, 1.42) | 0.87 ( 0.51, 1.47) | -0.01 | (-0.06, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9222 |
| No | 161 | 14 | 8.7 | 168 | 10 | 6.0 | 0.3388 | 0.68 ( 0.31, 1.50) | 0.66 ( 0.29, 1.54) | -0.03 | (-0.08, 0.03) | |
| Yes | 1113 | 81 | 7.3 | 1110 | 53 | 4.8 | 0.0132 | 0.66 ( 0.47, 0.92) | 0.64 ( 0.45, 0.91) | -0.03 | (-0.04,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6145 |
| No | 62 | 7 | 11.3 | 72 | 4 | 5.6 | 0.2279 | 0.49 ( 0.15, 1.60) | 0.46 ( 0.13, 1.66) | -0.06 | (-0.15, 0.04) | |
| Yes | 1212 | 88 | 7.3 | 1206 | 59 | 4.9 | 0.0148 | 0.67 ( 0.49, 0.93) | 0.66 ( 0.47, 0.92) | -0.02 | (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.6770 |
| No | 46 | 2 | 4.3 | 57 | 1 | 1.8 | 0.4365 | 0.40 ( 0.04, 4.31) | 0.39 ( 0.03, 4.47) | -0.03 | (-0.09, 0.04) | |
| Yes | 1228 | 93 | 7.6 | 1221 | 62 | 5.1 | 0.0112 | 0.67 ( 0.49, 0.92) | 0.65 ( 0.47, 0.91) | -0.02 | (-0.04,-0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 4 | 0.3 | 1278 | 1 | 0.1 | 0.1782 | 0.25 ( 0.03, 2.23) | 0.25 ( 0.03, 2.23) | 0.00 (-0.01, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 958 | 4 | 0.4 | 975 | 1 | 0.1 | | | | | |
| Female | 316 | 0 | 0 | 303 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 1 | 0.2 | 392 | 0 | 0 | | | | | |
| >=65 | 839 | 3 | 0.4 | 886 | 1 | 0.1 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 1 | 0.6 | | | | | |
| Latin America | 420 | 0 | 0 | 440 | 0 | 0 | | | | | |
| Europe | 469 | 1 | 0.2 | 467 | 0 | 0 | | | | | |
| Asia | 174 | 2 | 1.1 | 165 | 0 | 0 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 0 | 0 | 698 | 1 | 0.1 | | | | | |
| Non-Diabetic | 580 | 4 | 0.7 | 580 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 3 | 0.3 | 836 | 1 | 0.1 | | | | | |
| >=30 | 385 | 1 | 0.3 | 442 | 0 | 0 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 4 | 0.5 | 834 | 1 | 0.1 | | | | | |
| >=130 | 417 | 0 | 0 | 444 | 0 | 0 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 3 | 0.4 | 678 | 1 | 0.1 | | | | | |
| 75 to <85 | 348 | 0 | 0 | 382 | 0 | 0 | | | | | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 1 | 0.9 | | | | | |
| 30 to <45 | 348 | 3 | 0.9 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 1 | 0.1 | 818 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 3 | 0.7 | 456 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 1 | 0.2 | 608 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 189 | 0 | 0 | 207 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 3 | 0.3 | 947 | 0 | 0 | | | | | |
| Very high | 315 | 1 | 0.3 | 325 | 1 | 0.3 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 2 | 1.2 | 168 | 1 | 0.6 | | | | | |
| Yes | 1113 | 2 | 0.2 | 1110 | 0 | 0 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 3 | 0.2 | 1206 | 1 | 0.1 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 0 | 0 | | | | | |
| Yes | 1228 | 4 | 0.3 | 1221 | 1 | 0.1 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 3 | 0.2 | 1278 | 7 | 0.5 | 0.2068 | 2.33 ( 0.60, 8.97) | 2.33 ( 0.60, 9.04) | 0.00 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | |
| Male | 958 | 3 | 0.3 | 975 | 5 | 0.5 | | | | | |
| Female | 316 | 0 | 0 | 303 | 2 | 0.7 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 1 | 0.2 | 392 | 3 | 0.8 | | | | | |
| >=65 | 839 | 2 | 0.2 | 886 | 4 | 0.5 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 3 | 1.9 | | | | | |
| Latin America | 420 | 1 | 0.2 | 440 | 3 | 0.7 | | | | | |
| Europe | 469 | 0 | 0 | 467 | 1 | 0.2 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | |
| Other | 50 | 1 | 2.0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | 0.6906 |
| Diabetic | 694 | 3 | 0.4 | 698 | 7 | 1.0 | 0.2075 | 2.32 ( 0.60, 8.93) | 2.33 ( 0.60, 9.06) | 0.01 ( 0.00, 0.01) | |
| Non-Diabetic | 580 | 0 | 0 | 580 | 0 | 0 | 1.0000 | 1.00 ( 0.02, 50.31) | 1.00 ( 0.02, 50.48) | 0.00 ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 2 | 0.2 | 836 | 4 | 0.5 | | | | | |
| >=30 | 385 | 1 | 0.3 | 442 | 3 | 0.7 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 2 | 0.2 | 834 | 3 | 0.4 | | | | | |
| >=130 | 417 | 1 | 0.2 | 444 | 4 | 0.9 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 2 | 0.3 | 678 | 3 | 0.4 | | | | | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 3 | 0.8 | | | | | |
| >=85 | 208 | 0 | 0 | 218 | 1 | 0.5 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 2 | 1.7 | | | | | |
| 30 to <45 | 348 | 1 | 0.3 | 345 | 2 | 0.6 | | | | | |
| >=45 | 837 | 2 | 0.2 | 818 | 3 | 0.4 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 1 | 0.2 | 456 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 1 | 0.2 | 608 | 2 | 0.3 | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 4 | 1.9 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 3 | 0.3 | 947 | 3 | 0.3 | | | | | |
| Very high | 315 | 0 | 0 | 325 | 4 | 1.2 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 0 | 0 | 168 | 1 | 0.6 | | | | | |
| Yes | 1113 | 3 | 0.3 | 1110 | 6 | 0.5 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 2 | 0.2 | 1206 | 7 | 0.6 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | 0.6137 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 ( 0.02, 40.07) | 0.81 ( 0.02, 41.54) | 0.00 (-0.04, 0.04) | |
| Yes | 1228 | 3 | 0.2 | 1221 | 7 | 0.6 | 0.2018 | 2.35 ( 0.61, 9.05) | 2.35 ( 0.61, 9.13) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 10 | 0.8 | 1278 | 2 | 0.2 | 0.0203 | 0.20 ( 0.04, 0.91) | 0.20 ( 0.04, 0.91) | -0.01 (-0.01, 0.00) | | |
| Sex | | | | | | | | | | | | 0.7971 |
| Male | 958 | 9 | 0.9 | 975 | 2 | 0.2 | 0.0319 | 0.22 ( 0.05, 1.01) | 0.22 ( 0.05, 1.01) | -0.01 (-0.01, 0.00) | | |
| Female | 316 | 1 | 0.3 | 303 | 0 | 0 | 0.4973 | 0.35 ( 0.01, 8.50) | 0.35 ( 0.01, 8.54) | 0.00 (-0.01, 0.01) | | |
| Age [years] | | | | | | | | | | | | |
| <65 | 435 | 3 | 0.7 | 392 | 1 | 0.3 | | | | | | |
| >=65 | 839 | 7 | 0.8 | 886 | 1 | 0.1 | | | | | | |
| Region | | | | | | | | | | | | |
| North America | 161 | 2 | 1.2 | 159 | 0 | 0 | | | | | | |
| Latin America | 420 | 2 | 0.5 | 440 | 1 | 0.2 | | | | | | |
| Europe | 469 | 6 | 1.3 | 467 | 1 | 0.2 | | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | |
| Diabetic | 694 | 7 | 1.0 | 698 | 2 | 0.3 | | | | | | |
| Non-Diabetic | 580 | 3 | 0.5 | 580 | 0 | 0 | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | |
| <30 | 889 | 8 | 0.9 | 836 | 1 | 0.1 | | | | | | |
| >=30 | 385 | 2 | 0.5 | 442 | 1 | 0.2 | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 857 | 8 | 0.9 | 834 | 0 | 0 | | | | | | |
| >=130 | 417 | 2 | 0.5 | 444 | 2 | 0.5 | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 718 | 8 | 1.1 | 678 | 0 | 0 | | | | | | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 1 | 0.3 | | | | | | |
| >=85 | 208 | 1 | 0.5 | 218 | 1 | 0.5 | | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 0 | 0 | | | | | |
| 30 to <45 | 348 | 6 | 1.7 | 345 | 1 | 0.3 | | | | | |
| >=45 | 837 | 4 | 0.5 | 818 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 5 | 1.1 | 456 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 5 | 0.8 | 608 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 189 | 0 | 0 | 207 | 1 | 0.5 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 6 | 0.6 | 947 | 1 | 0.1 | | | | | |
| Very high | 315 | 4 | 1.3 | 325 | 1 | 0.3 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.2214 |
| No | 161 | 1 | 0.6 | 168 | 1 | 0.6 | 0.9759 | 0.96 ( 0.06, 15.19) | 0.96 ( 0.06, 15.45) | 0.00 (-0.02, 0.02) | |
| Yes | 1113 | 9 | 0.8 | 1110 | 1 | 0.1 | 0.0114 | 0.11 ( 0.01, 0.88) | 0.11 ( 0.01, 0.87) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.8883 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 ( 0.01, 6.94) | 0.28 ( 0.01, 7.07) | -0.02 (-0.06, 0.03) | |
| Yes | 1212 | 9 | 0.7 | 1206 | 2 | 0.2 | 0.0351 | 0.22 ( 0.05, 1.03) | 0.22 ( 0.05, 1.03) | -0.01 (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.5141 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 ( 0.02, 40.07) | 0.81 ( 0.02, 41.54) | 0.00 (-0.04, 0.04) | |
| Yes | 1228 | 10 | 0.8 | 1221 | 2 | 0.2 | 0.0212 | 0.20 ( 0.04, 0.92) | 0.20 ( 0.04, 0.91) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 6 | 0.5 | 1278 | 9 | 0.7 | 0.4408 | 1.50 ( 0.53, 4.19) | 1.50 ( 0.53, 4.22) | 0.00 ( 0.00,0.01) | |
| Sex | | | | | | | | | | | 0.3315 |
| Male | 958 | 4 | 0.4 | 975 | 8 | 0.8 | 0.2594 | 1.97 ( 0.59, 6.50) | 1.97 ( 0.59, 6.57) | 0.00 ( 0.00,0.01) | |
| Female | 316 | 2 | 0.6 | 303 | 1 | 0.3 | 0.5875 | 0.52 ( 0.05, 5.72) | 0.52 ( 0.05, 5.76) | 0.00 (-0.01,0.01) | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 3 | 0.7 | 392 | 4 | 1.0 | | | | | |
| >=65 | 839 | 3 | 0.4 | 886 | 5 | 0.6 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 1 | 0.6 | | | | | |
| Latin America | 420 | 2 | 0.5 | 440 | 4 | 0.9 | | | | | |
| Europe | 469 | 3 | 0.6 | 467 | 4 | 0.9 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | 0.7605 |
| Diabetic | 694 | 5 | 0.7 | 698 | 8 | 1.1 | 0.4091 | 1.59 ( 0.52, 4.84) | 1.60 ( 0.52, 4.91) | 0.00 (-0.01,0.01) | |
| Non-Diabetic | 580 | 1 | 0.2 | 580 | 1 | 0.2 | 1.0000 | 1.00 ( 0.06, 15.95) | 1.00 ( 0.06, 16.03) | 0.00 ( 0.00,0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 2 | 0.2 | 836 | 6 | 0.7 | | | | | |
| >=30 | 385 | 4 | 1.0 | 442 | 3 | 0.7 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 4 | 0.5 | 834 | 5 | 0.6 | | | | | |
| >=130 | 417 | 2 | 0.5 | 444 | 4 | 0.9 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 2 | 0.3 | 678 | 6 | 0.9 | | | | | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 1 | 0.3 | | | | | |
| >=85 | 208 | 3 | 1.4 | 218 | 2 | 0.9 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 1 | 0.9 | | | | | | | |
| 30 to <45 | 348 | 2 | 0.6 | 345 | 3 | 0.9 | | | | | | | |
| >=45 | 837 | 4 | 0.5 | 818 | 5 | 0.6 | | | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | |
| Normal (<30) | 452 | 0 | 0 | 456 | 3 | 0.7 | | | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 3 | 0.5 | 608 | 3 | 0.5 | | | | | | | |
| Macroalbuminuria (>300) | 189 | 3 | 1.6 | 207 | 3 | 1.4 | | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | | |
| Low, moderate or high | 953 | 2 | 0.2 | 947 | 7 | 0.7 | | | | | | | |
| Very high | 315 | 4 | 1.3 | 325 | 2 | 0.6 | | | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.1369 |
| No | 161 | 2 | 1.2 | 168 | 0 | 0 | 0.2313 | 0.19 | (<0.01, 3.96) | 0.19 | (<0.01, 3.97) | -0.01 | (-0.03,0.01) |
| Yes | 1113 | 4 | 0.4 | 1110 | 9 | 0.8 | 0.1628 | 2.26 | ( 0.70, 7.30) | 2.27 | ( 0.70, 7.38) | 0.00 | ( 0.00,0.01) |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.7003 |
| No | 62 | 0 | 0 | 72 | 1 | 1.4 | 0.5424 | 2.59 | ( 0.11, 62.43) | 2.62 | ( 0.10, 65.54) | 0.01 | (-0.03,0.05) |
| Yes | 1212 | 6 | 0.5 | 1206 | 8 | 0.7 | 0.5855 | 1.34 | ( 0.47, 3.85) | 1.34 | ( 0.46, 3.88) | 0.00 | ( 0.00,0.01) |
| Baseline use of diuretics | | | | | | | | | | | | | 0.7627 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 | ( 0.02, 40.07) | 0.81 | ( 0.02, 41.54) | 0.00 | (-0.04,0.04) |
| Yes | 1228 | 6 | 0.5 | 1221 | 9 | 0.7 | 0.4306 | 1.51 | ( 0.54, 4.23) | 1.51 | ( 0.54, 4.26) | 0.00 | ( 0.00,0.01) |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 10 | 0.8 | 1278 | 6 | 0.5 | 0.3128 | 0.60 | ( 0.22, 1.64) | 0.60 | ( 0.22, 1.65) | 0.00 | (-0.01,0.00) | |
| Sex | | | | | | | | | | | | | | 0.4409 |
| Male | 958 | 8 | 0.8 | 975 | 6 | 0.6 | 0.5690 | 0.74 | ( 0.26, 2.12) | 0.74 | ( 0.25, 2.13) | 0.00 | (-0.01,0.01) | |
| Female | 316 | 2 | 0.6 | 303 | 0 | 0 | 0.2621 | 0.21 | ( 0.01, 4.33) | 0.21 | (<0.01, 4.33) | -0.01 | (-0.02,0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.4777 |
| <65 | 435 | 2 | 0.5 | 392 | 0 | 0 | 0.2854 | 0.22 | ( 0.01, 4.61) | 0.22 | ( 0.01, 4.62) | 0.00 | (-0.01,0.00) | |
| >=65 | 839 | 8 | 1.0 | 886 | 6 | 0.7 | 0.5226 | 0.71 | ( 0.25, 2.04) | 0.71 | ( 0.24, 2.05) | 0.00 | (-0.01,0.01) | |
| Region | | | | | | | | | | | | | | |
| North America | 161 | 2 | 1.2 | 159 | 0 | 0 | | | | | | | | |
| Latin America | 420 | 3 | 0.7 | 440 | 2 | 0.5 | | | | | | | | |
| Europe | 469 | 4 | 0.9 | 467 | 3 | 0.6 | | | | | | | | |
| Asia | 174 | 1 | 0.6 | 165 | 1 | 0.6 | | | | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7935 |
| Diabetic | 694 | 6 | 0.9 | 698 | 4 | 0.6 | 0.5197 | 0.66 | ( 0.19, 2.34) | 0.66 | ( 0.19, 2.35) | 0.00 | (-0.01,0.01) | |
| Non-Diabetic | 580 | 4 | 0.7 | 580 | 2 | 0.3 | 0.4130 | 0.50 | ( 0.09, 2.72) | 0.50 | ( 0.09, 2.73) | 0.00 | (-0.01,0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1333 |
| <30 | 889 | 9 | 1.0 | 836 | 3 | 0.4 | 0.1027 | 0.35 | ( 0.10, 1.30) | 0.35 | ( 0.10, 1.31) | -0.01 | (-0.01,0.00) | |
| >=30 | 385 | 1 | 0.3 | 442 | 3 | 0.7 | 0.3863 | 2.61 | ( 0.27, 25.02) | 2.62 | ( 0.27, 25.33) | 0.00 | ( 0.00,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9536 |
| <130 | 857 | 7 | 0.8 | 834 | 4 | 0.5 | 0.3885 | 0.59 | ( 0.17, 2.00) | 0.59 | ( 0.17, 2.01) | 0.00 | (-0.01,0.00) | |
| >=130 | 417 | 3 | 0.7 | 444 | 2 | 0.5 | 0.6037 | 0.63 | ( 0.11, 3.73) | 0.62 | ( 0.10, 3.76) | 0.00 | (-0.01,0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | |
| <75 | 718 | 5 | 0.7 | 678 | 4 | 0.6 | | | | | | | | |
| 75 to <85 | 348 | 3 | 0.9 | 382 | 0 | 0 | | | | | | | | |
| >=85 | 208 | 2 | 1.0 | 218 | 2 | 0.9 | | | | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1139 |
| <30 | 89 | 1 | 1.1 | 115 | 0 | 0 | 0.3697 | 0.26 | ( 0.01, 6.27) | 0.26 | ( 0.01, 6.35) | -0.01 | (-0.04,0.02) | |
| 30 to <45 | 348 | 1 | 0.3 | 345 | 4 | 1.2 | 0.1750 | 4.03 | ( 0.45, 35.92) | 4.07 | ( 0.45, 36.60) | 0.01 | ( 0.00,0.02) | |
| >=45 | 837 | 8 | 1.0 | 818 | 2 | 0.2 | 0.0619 | 0.26 | ( 0.05, 1.20) | 0.25 | ( 0.05, 1.20) | -0.01 | (-0.01,0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8192 |
| Normal (<30) | 452 | 3 | 0.7 | 456 | 1 | 0.2 | 0.3120 | 0.33 | ( 0.03, 3.16) | 0.33 | ( 0.03, 3.17) | 0.00 | (-0.01,0.00) | |
| Microalbuminuria (30 to <=300) | 627 | 6 | 1.0 | 608 | 4 | 0.7 | 0.5577 | 0.69 | ( 0.19, 2.42) | 0.69 | ( 0.19, 2.44) | 0.00 | (-0.01,0.01) | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 1 | 0.5 | 0.9486 | 0.91 | ( 0.06, 14.50) | 0.91 | ( 0.06, 14.69) | 0.00 | (-0.01,0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0807 |
| Low, moderate or high | 953 | 8 | 0.8 | 947 | 2 | 0.2 | 0.0584 | 0.25 | ( 0.05, 1.18) | 0.25 | ( 0.05, 1.18) | -0.01 | (-0.01,0.00) | |
| Very high | 315 | 2 | 0.6 | 325 | 4 | 1.2 | 0.4342 | 1.94 | ( 0.36, 10.51) | 1.95 | ( 0.35, 10.72) | 0.01 | (-0.01,0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4036 |
| No | 161 | 2 | 1.2 | 168 | 0 | 0 | 0.2313 | 0.19 | (<0.01, 3.96) | 0.19 | (<0.01, 3.97) | -0.01 | (-0.03,0.01) | |
| Yes | 1113 | 8 | 0.7 | 1110 | 6 | 0.5 | 0.5953 | 0.75 | ( 0.26, 2.16) | 0.75 | ( 0.26, 2.17) | 0.00 | (-0.01,0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6204 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 | ( 0.01, 6.94) | 0.28 | ( 0.01, 7.07) | -0.02 | (-0.06,0.03) | |
| Yes | 1212 | 9 | 0.7 | 1206 | 6 | 0.5 | 0.4429 | 0.67 | ( 0.24, 1.88) | 0.67 | ( 0.24, 1.88) | 0.00 | (-0.01,0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8860 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 | ( 0.02, 40.07) | 0.81 | ( 0.02, 41.54) | 0.00 | (-0.04,0.04) | |
| Yes | 1228 | 10 | 0.8 | 1221 | 6 | 0.5 | 0.3213 | 0.60 | ( 0.22, 1.66) | 0.60 | ( 0.22, 1.66) | 0.00 | (-0.01,0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
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Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 1 | 0.1 | 1278 | 0 | 0 | 0.4780 | 0.33 | ( 0.01, 8.15) | 0.33 | ( 0.01, 8.16) | 0.00 ( 0.00,0.00) | |
| Sex | | | | | | | | | | | | | |
| Male | 958 | 1 | 0.1 | 975 | 0 | 0 | | | | | | | |
| Female | 316 | 0 | 0 | 303 | 0 | 0 | | | | | | | |
| Age [years] | | | | | | | | | | | | | |
| <65 | 435 | 1 | 0.2 | 392 | 0 | 0 | | | | | | | |
| >=65 | 839 | 0 | 0 | 886 | 0 | 0 | | | | | | | |
| Region | | | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 0 | 0 | | | | | | | |
| Latin America | 420 | 0 | 0 | 440 | 0 | 0 | | | | | | | |
| Europe | 469 | 0 | 0 | 467 | 0 | 0 | | | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | |
| Diabetic | 694 | 1 | 0.1 | 698 | 0 | 0 | | | | | | | |
| Non-Diabetic | 580 | 0 | 0 | 580 | 0 | 0 | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | |
| <30 | 889 | 1 | 0.1 | 836 | 0 | 0 | | | | | | | |
| >=30 | 385 | 0 | 0 | 442 | 0 | 0 | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | |
| <130 | 857 | 0 | 0 | 834 | 0 | 0 | | | | | | | |
| >=130 | 417 | 1 | 0.2 | 444 | 0 | 0 | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | |
| <75 | 718 | 0 | 0 | 678 | 0 | 0 | | | | | | | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 0 | 0 | | | | | | | |
| >=85 | 208 | 0 | 0 | 218 | 0 | 0 | | | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 0 | 0 | | | | | |
| 30 to <45 | 348 | 0 | 0 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 1 | 0.1 | 818 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 0 | 0 | 456 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 0 | 0 | 608 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 1 | 0.1 | 947 | 0 | 0 | | | | | |
| Very high | 315 | 0 | 0 | 325 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 0 | 0 | 168 | 0 | 0 | | | | | |
| Yes | 1113 | 1 | 0.1 | 1110 | 0 | 0 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 0 | 0 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 1 | 0.1 | 1206 | 0 | 0 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 0 | 0 | | | | | |
| Yes | 1228 | 1 | 0.1 | 1221 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 7 | 0.5 | 1278 | 6 | 0.5 | 0.7766 | 0.85 | ( 0.29, 2.54) | 0.85 | ( 0.29, 2.55) | 0.00 | (-0.01,0.00) | |
| Sex | | | | | | | | | | | | | | 0.4018 |
| Male | 958 | 6 | 0.6 | 975 | 4 | 0.4 | 0.5080 | 0.66 | ( 0.19, 2.31) | 0.65 | ( 0.18, 2.32) | 0.00 | (-0.01,0.00) | |
| Female | 316 | 1 | 0.3 | 303 | 2 | 0.7 | 0.5383 | 2.09 | ( 0.19, 22.88) | 2.09 | ( 0.19, 23.20) | 0.00 | (-0.01,0.01) | |
| Age [years] | | | | | | | | | | | | | | |
| <65 | 435 | 3 | 0.7 | 392 | 2 | 0.5 | | | | | | | | |
| >=65 | 839 | 4 | 0.5 | 886 | 4 | 0.5 | | | | | | | | |
| Region | | | | | | | | | | | | | | |
| North America | 161 | 2 | 1.2 | 159 | 2 | 1.3 | | | | | | | | |
| Latin America | 420 | 3 | 0.7 | 440 | 3 | 0.7 | | | | | | | | |
| Europe | 469 | 1 | 0.2 | 467 | 1 | 0.2 | | | | | | | | |
| Asia | 174 | 1 | 0.6 | 165 | 0 | 0 | | | | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9386 |
| Diabetic | 694 | 7 | 1.0 | 698 | 6 | 0.9 | 0.7725 | 0.85 | ( 0.29, 2.52) | 0.85 | ( 0.28, 2.54) | 0.00 | (-0.01,0.01) | |
| Non-Diabetic | 580 | 0 | 0 | 580 | 0 | 0 | 1.0000 | 1.00 | ( 0.02, 50.31) | 1.00 | ( 0.02, 50.48) | 0.00 | ( 0.00,0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | |
| <30 | 889 | 5 | 0.6 | 836 | 1 | 0.1 | | | | | | | | |
| >=30 | 385 | 2 | 0.5 | 442 | 5 | 1.1 | | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | |
| <130 | 857 | 3 | 0.4 | 834 | 3 | 0.4 | | | | | | | | |
| >=130 | 417 | 4 | 1.0 | 444 | 3 | 0.7 | | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | |
| <75 | 718 | 5 | 0.7 | 678 | 2 | 0.3 | | | | | | | | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 4 | 1.0 | | | | | | | | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | | | | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 2 | 1.7 | | | | | | | |
| 30 to <45 | 348 | 4 | 1.1 | 345 | 2 | 0.6 | | | | | | | |
| >=45 | 837 | 3 | 0.4 | 818 | 2 | 0.2 | | | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | |
| Normal (<30) | 452 | 3 | 0.7 | 456 | 2 | 0.4 | | | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 2 | 0.3 | 608 | 1 | 0.2 | | | | | | | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 207 | 3 | 1.4 | | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | | |
| Low, moderate or high | 953 | 6 | 0.6 | 947 | 3 | 0.3 | | | | | | | |
| Very high | 315 | 1 | 0.3 | 325 | 3 | 0.9 | | | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.4219 |
| No | 161 | 0 | 0 | 168 | 1 | 0.6 | 0.4969 | 2.88 | ( 0.12, 70.08) | 2.89 | ( 0.12, 71.52) | 0.01 (-0.01,0.02) | |
| Yes | 1113 | 7 | 0.6 | 1110 | 5 | 0.5 | 0.5658 | 0.72 | ( 0.23, 2.25) | 0.71 | ( 0.23, 2.26) | 0.00 (-0.01,0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.4678 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 | ( 0.01, 6.94) | 0.28 | ( 0.01, 7.07) | -0.02 (-0.06,0.03) | |
| Yes | 1212 | 6 | 0.5 | 1206 | 6 | 0.5 | 0.9931 | 1.00 | ( 0.33, 3.11) | 1.01 | ( 0.32, 3.12) | 0.00 (-0.01,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.9761 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 | ( 0.02, 40.07) | 0.81 | ( 0.02, 41.54) | 0.00 (-0.04,0.04) | |
| Yes | 1228 | 7 | 0.6 | 1221 | 6 | 0.5 | 0.7889 | 0.86 | ( 0.29, 2.56) | 0.86 | ( 0.29, 2.57) | 0.00 (-0.01,0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 9 | 0.7 | 1278 | 7 | 0.5 | 0.6115 | 0.78 | ( 0.29, 2.08) | 0.77 | ( 0.29, 2.08) | 0.00 | (-0.01,0.00) | |
| Sex | | | | | | | | | | | | | | 0.3531 |
| Male | 958 | 7 | 0.7 | 975 | 4 | 0.4 | 0.3491 | 0.56 | ( 0.16, 1.91) | 0.56 | ( 0.16, 1.92) | 0.00 | (-0.01,0.00) | |
| Female | 316 | 2 | 0.6 | 303 | 3 | 1.0 | 0.6197 | 1.56 | ( 0.26, 9.30) | 1.57 | ( 0.26, 9.46) | 0.00 | (-0.01,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.6684 |
| <65 | 435 | 2 | 0.5 | 392 | 2 | 0.5 | 0.9169 | 1.11 | ( 0.16, 7.84) | 1.11 | ( 0.16, 7.92) | 0.00 | (-0.01,0.01) | |
| >=65 | 839 | 7 | 0.8 | 886 | 5 | 0.6 | 0.5001 | 0.68 | ( 0.22, 2.12) | 0.67 | ( 0.21, 2.13) | 0.00 | (-0.01,0.01) | |
| Region | | | | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 0 | 0 | | | | | | | | |
| Latin America | 420 | 3 | 0.7 | 440 | 2 | 0.5 | | | | | | | | |
| Europe | 469 | 4 | 0.9 | 467 | 5 | 1.1 | | | | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | | | | |
| Other | 50 | 1 | 2.0 | 47 | 0 | 0 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | |
| Diabetic | 694 | 5 | 0.7 | 698 | 4 | 0.6 | | | | | | | | |
| Non-Diabetic | 580 | 4 | 0.7 | 580 | 3 | 0.5 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8426 |
| <30 | 889 | 6 | 0.7 | 836 | 4 | 0.5 | 0.5912 | 0.71 | ( 0.20, 2.50) | 0.71 | ( 0.20, 2.52) | 0.00 | (-0.01,0.01) | |
| >=30 | 385 | 3 | 0.8 | 442 | 3 | 0.7 | 0.8651 | 0.87 | ( 0.18, 4.29) | 0.87 | ( 0.17, 4.34) | 0.00 | (-0.01,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7610 |
| <130 | 857 | 6 | 0.7 | 834 | 4 | 0.5 | 0.5544 | 0.69 | ( 0.19, 2.42) | 0.68 | ( 0.19, 2.43) | 0.00 | (-0.01,0.01) | |
| >=130 | 417 | 3 | 0.7 | 444 | 3 | 0.7 | 0.9385 | 0.94 | ( 0.19, 4.63) | 0.94 | ( 0.19, 4.68) | 0.00 | (-0.01,0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2749 |
| <75 | 718 | 8 | 1.1 | 678 | 4 | 0.6 | 0.2889 | 0.53 | ( 0.16, 1.75) | 0.53 | ( 0.16, 1.76) | -0.01 | (-0.01,0.00) | |
| 75 to <85 | 348 | 0 | 0 | 382 | 3 | 0.8 | 0.1578 | 6.38 | ( 0.33,123.05) | 6.43 | ( 0.33,124.89) | 0.01 | ( 0.00,0.02) | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | 0.4580 | 0.32 | ( 0.01, 7.77) | 0.32 | ( 0.01, 7.81) | 0.00 | (-0.02,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | |
| <30 | 89 | 1 | 1.1 | 115 | 2 | 1.7 | | | | | | | | |
| 30 to <45 | 348 | 3 | 0.9 | 345 | 1 | 0.3 | | | | | | | | |
| >=45 | 837 | 5 | 0.6 | 818 | 4 | 0.5 | | | | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | |
| Normal (<30) | 452 | 3 | 0.7 | 456 | 3 | 0.7 | | | | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 4 | 0.6 | 608 | 3 | 0.5 | | | | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 1 | 0.5 | | | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9012 |
| Low, moderate or high | 953 | 6 | 0.6 | 947 | 5 | 0.5 | 0.7704 | 0.84 | ( 0.26, 2.74) | 0.84 | ( 0.25, 2.75) | 0.00 | (-0.01,0.01) | |
| Very high | 315 | 2 | 0.6 | 325 | 2 | 0.6 | 0.9750 | 0.97 | ( 0.14, 6.84) | 0.97 | ( 0.14, 6.92) | 0.00 | (-0.01,0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5545 |
| No | 161 | 1 | 0.6 | 168 | 0 | 0 | 0.4597 | 0.32 | ( 0.01, 7.79) | 0.32 | ( 0.01, 7.85) | -0.01 | (-0.02,0.01) | |
| Yes | 1113 | 8 | 0.7 | 1110 | 7 | 0.6 | 0.7996 | 0.88 | ( 0.32, 2.41) | 0.88 | ( 0.32, 2.43) | 0.00 | (-0.01,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5120 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 | ( 0.01, 6.94) | 0.28 | ( 0.01, 7.07) | -0.02 | (-0.06,0.03) | |
| Yes | 1212 | 8 | 0.7 | 1206 | 7 | 0.6 | 0.8031 | 0.88 | ( 0.32, 2.42) | 0.88 | ( 0.32, 2.43) | 0.00 | (-0.01,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9863 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 | ( 0.02, 40.07) | 0.81 | ( 0.02, 41.54) | 0.00 | (-0.04,0.04) | |
| Yes | 1228 | 9 | 0.7 | 1221 | 7 | 0.6 | 0.6240 | 0.78 | ( 0.29, 2.09) | 0.78 | ( 0.29, 2.10) | 0.00 | (-0.01,0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 0 | 0 | 1278 | 0 | 0 | | | | | |
| Sex | | | | | | | | | | | |
| Male | 958 | 0 | 0 | 975 | 0 | 0 | | | | | |
| Female | 316 | 0 | 0 | 303 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 0 | 0 | 392 | 0 | 0 | | | | | |
| >=65 | 839 | 0 | 0 | 886 | 0 | 0 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 0 | 0 | 159 | 0 | 0 | | | | | |
| Latin America | 420 | 0 | 0 | 440 | 0 | 0 | | | | | |
| Europe | 469 | 0 | 0 | 467 | 0 | 0 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 0 | 0 | 698 | 0 | 0 | | | | | |
| Non-Diabetic | 580 | 0 | 0 | 580 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 0 | 0 | 836 | 0 | 0 | | | | | |
| >=30 | 385 | 0 | 0 | 442 | 0 | 0 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 0 | 0 | 834 | 0 | 0 | | | | | |
| >=130 | 417 | 0 | 0 | 444 | 0 | 0 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 0 | 0 | 678 | 0 | 0 | | | | | |
| 75 to <85 | 348 | 0 | 0 | 382 | 0 | 0 | | | | | |
| >=85 | 208 | 0 | 0 | 218 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 0 | 0 | | | | | |
| 30 to <45 | 348 | 0 | 0 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 0 | 0 | 818 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 0 | 0 | 456 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 0 | 0 | 608 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 189 | 0 | 0 | 207 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 0 | 0 | 947 | 0 | 0 | | | | | |
| Very high | 315 | 0 | 0 | 325 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 0 | 0 | 168 | 0 | 0 | | | | | |
| Yes | 1113 | 0 | 0 | 1110 | 0 | 0 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 0 | 0 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 0 | 0 | 1206 | 0 | 0 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 0 | 0 | | | | | |
| Yes | 1228 | 0 | 0 | 1221 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 3 | 0.2 | 1278 | 3 | 0.2 | 0.9969 | 1.00 ( 0.20, 4.93) | 1.00 ( 0.20, 4.95) | 0.00 ( 0.00,0.00) | |
| Sex | | | | | | | | | | | |
| Male | 958 | 2 | 0.2 | 975 | 1 | 0.1 | | | | | |
| Female | 316 | 1 | 0.3 | 303 | 2 | 0.7 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 1 | 0.2 | 392 | 1 | 0.3 | | | | | |
| >=65 | 839 | 2 | 0.2 | 886 | 2 | 0.2 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 0 | 0 | 159 | 0 | 0 | | | | | |
| Latin America | 420 | 2 | 0.5 | 440 | 1 | 0.2 | | | | | |
| Europe | 469 | 1 | 0.2 | 467 | 2 | 0.4 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 0 | 0 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 2 | 0.3 | 698 | 1 | 0.1 | | | | | |
| Non-Diabetic | 580 | 1 | 0.2 | 580 | 2 | 0.3 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 1 | 0.1 | 836 | 2 | 0.2 | | | | | |
| >=30 | 385 | 2 | 0.5 | 442 | 1 | 0.2 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 1 | 0.1 | 834 | 1 | 0.1 | | | | | |
| >=130 | 417 | 2 | 0.5 | 444 | 2 | 0.5 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 3 | 0.4 | 678 | 2 | 0.3 | | | | | |
| 75 to <85 | 348 | 0 | 0 | 382 | 1 | 0.3 | | | | | |
| >=85 | 208 | 0 | 0 | 218 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 1 | 0.9 | | | | | |
| 30 to <45 | 348 | 0 | 0 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 3 | 0.4 | 818 | 2 | 0.2 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 1 | 0.2 | 456 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 0 | 0 | 608 | 2 | 0.3 | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 2 | 0.2 | 947 | 2 | 0.2 | | | | | |
| Very high | 315 | 0 | 0 | 325 | 1 | 0.3 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 0 | 0 | 168 | 0 | 0 | | | | | |
| Yes | 1113 | 3 | 0.3 | 1110 | 3 | 0.3 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 2 | 0.2 | 1206 | 3 | 0.2 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 0 | 0 | | | | | |
| Yes | 1228 | 3 | 0.2 | 1221 | 3 | 0.2 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 7 | 0.5 | 1278 | 10 | 0.8 | 0.4693 | 1.42 | ( 0.54, 3.73) | 1.43 | ( 0.54, 3.76) | 0.00 | ( 0.00,0.01) | |
| Sex | | | | | | | | | | | | | | 0.6257 |
| Male | 958 | 4 | 0.4 | 975 | 7 | 0.7 | 0.3800 | 1.72 | ( 0.50, 5.85) | 1.72 | ( 0.50, 5.91) | 0.00 | ( 0.00,0.01) | |
| Female | 316 | 3 | 0.9 | 303 | 3 | 1.0 | 0.9588 | 1.04 | ( 0.21, 5.13) | 1.04 | ( 0.21, 5.21) | 0.00 | (-0.02,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.4034 |
| <65 | 435 | 2 | 0.5 | 392 | 1 | 0.3 | 0.6250 | 0.55 | ( 0.05, 6.10) | 0.55 | ( 0.05, 6.13) | 0.00 | (-0.01,0.01) | |
| >=65 | 839 | 5 | 0.6 | 886 | 9 | 1.0 | 0.3313 | 1.70 | ( 0.57, 5.07) | 1.71 | ( 0.57, 5.13) | 0.00 | ( 0.00,0.01) | |
| Region | | | | | | | | | | | | | | 0.5187 |
| North America | 161 | 2 | 1.2 | 159 | 0 | 0 | 0.2504 | 0.20 | (<0.01, 4.18) | 0.20 | (<0.01, 4.20) | -0.01 | (-0.03,0.01) | |
| Latin America | 420 | 1 | 0.2 | 440 | 3 | 0.7 | 0.3391 | 2.86 | ( 0.30, 27.42) | 2.88 | ( 0.30, 27.76) | 0.00 | ( 0.00,0.01) | |
| Europe | 469 | 3 | 0.6 | 467 | 7 | 1.5 | 0.2011 | 2.34 | ( 0.61, 9.01) | 2.36 | ( 0.61, 9.20) | 0.01 | ( 0.00,0.02) | |
| Asia | 174 | 1 | 0.6 | 165 | 0 | 0 | 0.5016 | 0.35 | ( 0.01, 8.57) | 0.35 | ( 0.01, 8.64) | -0.01 | (-0.02,0.01) | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 | ( 0.02, 52.49) | 1.06 | ( 0.02, 54.66) | 0.00 | (-0.04,0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | |
| Diabetic | 694 | 5 | 0.7 | 698 | 3 | 0.4 | | | | | | | | |
| Non-Diabetic | 580 | 2 | 0.3 | 580 | 7 | 1.2 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4338 |
| <30 | 889 | 7 | 0.8 | 836 | 8 | 1.0 | 0.7047 | 1.22 | ( 0.44, 3.34) | 1.22 | ( 0.44, 3.37) | 0.00 | (-0.01,0.01) | |
| >=30 | 385 | 0 | 0 | 442 | 2 | 0.5 | 0.2984 | 4.36 | ( 0.21, 90.47) | 4.38 | ( 0.21, 91.42) | 0.00 | ( 0.00,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6895 |
| <130 | 857 | 5 | 0.6 | 834 | 6 | 0.7 | 0.7280 | 1.23 | ( 0.38, 4.02) | 1.23 | ( 0.38, 4.06) | 0.00 | (-0.01,0.01) | |
| >=130 | 417 | 2 | 0.5 | 444 | 4 | 0.9 | 0.4577 | 1.88 | ( 0.35, 10.20) | 1.89 | ( 0.34, 10.35) | 0.00 | (-0.01,0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5264 |
| <75 | 718 | 6 | 0.8 | 678 | 6 | 0.9 | 0.9206 | 1.06 | ( 0.34, 3.27) | 1.06 | ( 0.34, 3.30) | 0.00 | (-0.01,0.01) | |
| 75 to <85 | 348 | 0 | 0 | 382 | 3 | 0.8 | 0.1578 | 6.38 | ( 0.33,123.05) | 6.43 | ( 0.33,124.89) | 0.01 | ( 0.00,0.02) | |
| >=85 | 208 | 1 | 0.5 | 218 | 1 | 0.5 | 0.9734 | 0.95 | ( 0.06, 15.16) | 0.95 | ( 0.06, 15.35) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.9021 |
| <30 | 89 | 0 | 0 | 115 | 1 | 0.9 | 0.5923 | 2.33 ( 0.10, 56.46) | 2.34 ( 0.09, 58.25) | 0.01 (-0.02,0.03) | |
| 30 to <45 | 348 | 2 | 0.6 | 345 | 2 | 0.6 | 0.9931 | 1.01 ( 0.14, 7.12) | 1.01 ( 0.14, 7.20) | 0.00 (-0.01,0.01) | |
| >=45 | 837 | 5 | 0.6 | 818 | 7 | 0.9 | 0.5356 | 1.43 ( 0.46, 4.50) | 1.44 ( 0.45, 4.54) | 0.00 (-0.01,0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 3 | 0.7 | 456 | 3 | 0.7 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 2 | 0.3 | 608 | 6 | 1.0 | | | | | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 207 | 1 | 0.5 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.4781 |
| Low, moderate or high | 953 | 6 | 0.6 | 947 | 7 | 0.7 | 0.7720 | 1.17 ( 0.40, 3.48) | 1.18 ( 0.39, 3.51) | 0.00 (-0.01,0.01) | |
| Very high | 315 | 1 | 0.3 | 325 | 3 | 0.9 | 0.3311 | 2.91 ( 0.30, 27.81) | 2.93 ( 0.30, 28.27) | 0.01 (-0.01,0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.7645 |
| No | 161 | 1 | 0.6 | 168 | 1 | 0.6 | 0.9759 | 0.96 ( 0.06, 15.19) | 0.96 ( 0.06, 15.45) | 0.00 (-0.02,0.02) | |
| Yes | 1113 | 6 | 0.5 | 1110 | 9 | 0.8 | 0.4339 | 1.50 ( 0.54, 4.21) | 1.51 ( 0.54, 4.25) | 0.00 ( 0.00,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6826 |
| No | 62 | 0 | 0 | 72 | 1 | 1.4 | 0.5424 | 2.59 ( 0.11, 62.43) | 2.62 ( 0.10, 65.54) | 0.01 (-0.03,0.05) | |
| Yes | 1212 | 7 | 0.6 | 1206 | 9 | 0.7 | 0.6089 | 1.29 ( 0.48, 3.46) | 1.29 ( 0.48, 3.49) | 0.00 ( 0.00,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.7800 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 ( 0.02, 40.07) | 0.81 ( 0.02, 41.54) | 0.00 (-0.04,0.04) | |
| Yes | 1228 | 7 | 0.6 | 1221 | 10 | 0.8 | 0.4581 | 1.44 ( 0.55, 3.76) | 1.44 ( 0.55, 3.80) | 0.00 ( 0.00,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 4 | 0.3 | 1278 | 4 | 0.3 | 0.9965 | 1.00 ( 0.25, 3.98) | 1.00 ( 0.25, 3.99) | 0.00 ( 0.00,0.00) | |
| Sex | | | | | | | | | | | |
| Male | 958 | 2 | 0.2 | 975 | 4 | 0.4 | | | | | |
| Female | 316 | 2 | 0.6 | 303 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 1 | 0.2 | 392 | 1 | 0.3 | | | | | |
| >=65 | 839 | 3 | 0.4 | 886 | 3 | 0.3 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 2 | 1.2 | 159 | 1 | 0.6 | | | | | |
| Latin America | 420 | 0 | 0 | 440 | 1 | 0.2 | | | | | |
| Europe | 469 | 2 | 0.4 | 467 | 1 | 0.2 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 1 | 0.6 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 2 | 0.3 | 698 | 4 | 0.6 | | | | | |
| Non-Diabetic | 580 | 2 | 0.3 | 580 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 4 | 0.4 | 836 | 4 | 0.5 | | | | | |
| >=30 | 385 | 0 | 0 | 442 | 0 | 0 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 3 | 0.4 | 834 | 3 | 0.4 | | | | | |
| >=130 | 417 | 1 | 0.2 | 444 | 1 | 0.2 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 3 | 0.4 | 678 | 3 | 0.4 | | | | | |
| 75 to <85 | 348 | 0 | 0 | 382 | 1 | 0.3 | | | | | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 1 | 1.1 | 115 | 0 | 0 | | | | | |
| 30 to <45 | 348 | 0 | 0 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 3 | 0.4 | 818 | 4 | 0.5 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 0 | 0 | 456 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 3 | 0.5 | 608 | 2 | 0.3 | | | | | |
| Macroalbuminuria (>300) | 189 | 1 | 0.5 | 207 | 1 | 0.5 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 3 | 0.3 | 947 | 3 | 0.3 | | | | | |
| Very high | 315 | 1 | 0.3 | 325 | 1 | 0.3 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 0 | 0 | 168 | 1 | 0.6 | | | | | |
| Yes | 1113 | 4 | 0.4 | 1110 | 3 | 0.3 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 3 | 0.2 | 1206 | 4 | 0.3 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 1 | 1.8 | | | | | |
| Yes | 1228 | 4 | 0.3 | 1221 | 3 | 0.2 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 18 | 1.4 | 1278 | 14 | 1.1 | 0.4712 | 0.78 | ( 0.39, 1.55) | 0.77 | ( 0.38, 1.56) | 0.00 | (-0.01,0.01) | |
| Sex | | | | | | | | | | | | | | 0.3820 |
| Male | 958 | 15 | 1.6 | 975 | 10 | 1.0 | 0.2933 | 0.66 | ( 0.30, 1.45) | 0.65 | ( 0.29, 1.46) | -0.01 | (-0.02,0.00) | |
| Female | 316 | 3 | 0.9 | 303 | 4 | 1.3 | 0.6628 | 1.39 | ( 0.31, 6.16) | 1.40 | ( 0.31, 6.29) | 0.00 | (-0.01,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.7229 |
| <65 | 435 | 6 | 1.4 | 392 | 5 | 1.3 | 0.8965 | 0.92 | ( 0.28, 3.01) | 0.92 | ( 0.28, 3.05) | 0.00 | (-0.02,0.01) | |
| >=65 | 839 | 12 | 1.4 | 886 | 9 | 1.0 | 0.4327 | 0.71 | ( 0.30, 1.68) | 0.71 | ( 0.30, 1.69) | 0.00 | (-0.01,0.01) | |
| Region | | | | | | | | | | | | | | 0.8063 |
| North America | 161 | 7 | 4.3 | 159 | 6 | 3.8 | 0.7947 | 0.87 | ( 0.30, 2.53) | 0.86 | ( 0.28, 2.63) | -0.01 | (-0.05,0.04) | |
| Latin America | 420 | 4 | 1.0 | 440 | 5 | 1.1 | 0.7910 | 1.19 | ( 0.32, 4.41) | 1.20 | ( 0.32, 4.48) | 0.00 | (-0.01,0.02) | |
| Europe | 469 | 4 | 0.9 | 467 | 3 | 0.6 | 0.7086 | 0.75 | ( 0.17, 3.35) | 0.75 | ( 0.17, 3.38) | 0.00 | (-0.01,0.01) | |
| Asia | 174 | 3 | 1.7 | 165 | 0 | 0 | 0.1453 | 0.15 | (<0.01, 2.89) | 0.15 | (<0.01, 2.89) | -0.02 | (-0.04,0.01) | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 | ( 0.02, 52.49) | 1.06 | ( 0.02, 54.66) | 0.00 | (-0.04,0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3690 |
| Diabetic | 694 | 13 | 1.9 | 698 | 8 | 1.1 | 0.2658 | 0.61 | ( 0.26, 1.47) | 0.61 | ( 0.25, 1.47) | -0.01 | (-0.02,0.01) | |
| Non-Diabetic | 580 | 5 | 0.9 | 580 | 6 | 1.0 | 0.7619 | 1.20 | ( 0.37, 3.91) | 1.20 | ( 0.36, 3.96) | 0.00 | (-0.01,0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5143 |
| <30 | 889 | 13 | 1.5 | 836 | 11 | 1.3 | 0.7951 | 0.90 | ( 0.41, 2.00) | 0.90 | ( 0.40, 2.02) | 0.00 | (-0.01,0.01) | |
| >=30 | 385 | 5 | 1.3 | 442 | 3 | 0.7 | 0.3636 | 0.52 | ( 0.13, 2.17) | 0.52 | ( 0.12, 2.19) | -0.01 | (-0.02,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0928 |
| <130 | 857 | 13 | 1.5 | 834 | 14 | 1.7 | 0.7908 | 1.11 | ( 0.52, 2.34) | 1.11 | ( 0.52, 2.37) | 0.00 | (-0.01,0.01) | |
| >=130 | 417 | 5 | 1.2 | 444 | 0 | 0 | 0.0335 | 0.09 | (<0.01, 1.54) | 0.08 | (<0.01, 1.53) | -0.01 | (-0.02,0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8023 |
| <75 | 718 | 13 | 1.8 | 678 | 11 | 1.6 | 0.7869 | 0.90 | ( 0.40, 1.99) | 0.89 | ( 0.40, 2.01) | 0.00 | (-0.02,0.01) | |
| 75 to <85 | 348 | 4 | 1.1 | 382 | 3 | 0.8 | 0.6141 | 0.68 | ( 0.15, 3.03) | 0.68 | ( 0.15, 3.06) | 0.00 | (-0.02,0.01) | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | 0.4580 | 0.32 | ( 0.01, 7.77) | 0.32 | ( 0.01, 7.81) | 0.00 | (-0.02,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8322 |
| <30 | 89 | 1 | 1.1 | 115 | 2 | 1.7 | 0.7172 | 1.55 | ( 0.14, 16.80) | 1.56 | ( 0.14, 17.46) | 0.01 | (-0.03,0.04) | |
| 30 to <45 | 348 | 4 | 1.1 | 345 | 3 | 0.9 | 0.7126 | 0.76 | ( 0.17, 3.36) | 0.75 | ( 0.17, 3.40) | 0.00 | (-0.02,0.01) | |
| >=45 | 837 | 13 | 1.6 | 818 | 9 | 1.1 | 0.4212 | 0.71 | ( 0.30, 1.65) | 0.71 | ( 0.30, 1.66) | 0.00 | (-0.02,0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4340 |
| Normal (<30) | 452 | 3 | 0.7 | 456 | 2 | 0.4 | 0.6467 | 0.66 | ( 0.11, 3.94) | 0.66 | ( 0.11, 3.96) | 0.00 | (-0.01,0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 11 | 1.8 | 608 | 11 | 1.8 | 0.9419 | 1.03 | ( 0.45, 2.36) | 1.03 | ( 0.44, 2.40) | 0.00 | (-0.01,0.02) | |
| Macroalbuminuria (>300) | 189 | 4 | 2.1 | 207 | 1 | 0.5 | 0.1460 | 0.23 | ( 0.03, 2.02) | 0.22 | ( 0.02, 2.03) | -0.02 | (-0.04,0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4271 |
| Low, moderate or high | 953 | 14 | 1.5 | 947 | 9 | 1.0 | 0.3013 | 0.65 | ( 0.28, 1.49) | 0.64 | ( 0.28, 1.49) | -0.01 | (-0.02,0.00) | |
| Very high | 315 | 4 | 1.3 | 325 | 5 | 1.5 | 0.7729 | 1.21 | ( 0.33, 4.47) | 1.21 | ( 0.32, 4.57) | 0.00 | (-0.02,0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2383 |
| No | 161 | 2 | 1.2 | 168 | 4 | 2.4 | 0.4403 | 1.92 | ( 0.36, 10.32) | 1.94 | ( 0.35, 10.74) | 0.01 | (-0.02,0.04) | |
| Yes | 1113 | 16 | 1.4 | 1110 | 10 | 0.9 | 0.2393 | 0.63 | ( 0.29, 1.37) | 0.62 | ( 0.28, 1.38) | -0.01 | (-0.01,0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5251 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 | ( 0.01, 6.94) | 0.28 | ( 0.01, 7.07) | -0.02 | (-0.06,0.03) | |
| Yes | 1212 | 17 | 1.4 | 1206 | 14 | 1.2 | 0.5972 | 0.83 | ( 0.41, 1.67) | 0.83 | ( 0.41, 1.68) | 0.00 | (-0.01,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9861 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 | ( 0.02, 40.07) | 0.81 | ( 0.02, 41.54) | 0.00 | (-0.04,0.04) | |
| Yes | 1228 | 18 | 1.5 | 1221 | 14 | 1.1 | 0.4867 | 0.78 | ( 0.39, 1.57) | 0.78 | ( 0.39, 1.57) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 17 | 1.3 | 1278 | 12 | 0.9 | 0.3460 | 0.70 | ( 0.34, 1.47) | 0.70 | ( 0.33, 1.47) | 0.00 | (-0.01,0.00) | |
| Sex | | | | | | | | | | | | | | 0.3018 |
| Male | 958 | 14 | 1.5 | 975 | 8 | 0.8 | 0.1842 | 0.56 | ( 0.24, 1.33) | 0.56 | ( 0.23, 1.34) | -0.01 | (-0.02,0.00) | |
| Female | 316 | 3 | 0.9 | 303 | 4 | 1.3 | 0.6628 | 1.39 | ( 0.31, 6.16) | 1.40 | ( 0.31, 6.29) | 0.00 | (-0.01,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.9279 |
| <65 | 435 | 6 | 1.4 | 392 | 4 | 1.0 | 0.6373 | 0.74 | ( 0.21, 2.60) | 0.74 | ( 0.21, 2.63) | 0.00 | (-0.02,0.01) | |
| >=65 | 839 | 11 | 1.3 | 886 | 8 | 0.9 | 0.4169 | 0.69 | ( 0.28, 1.70) | 0.69 | ( 0.27, 1.71) | 0.00 | (-0.01,0.01) | |
| Region | | | | | | | | | | | | | | 0.7783 |
| North America | 161 | 6 | 3.7 | 159 | 6 | 3.8 | 0.9824 | 1.01 | ( 0.33, 3.07) | 1.01 | ( 0.32, 3.21) | 0.00 | (-0.04,0.04) | |
| Latin America | 420 | 4 | 1.0 | 440 | 4 | 0.9 | 0.9473 | 0.95 | ( 0.24, 3.79) | 0.95 | ( 0.24, 3.84) | 0.00 | (-0.01,0.01) | |
| Europe | 469 | 4 | 0.9 | 467 | 2 | 0.4 | 0.4157 | 0.50 | ( 0.09, 2.73) | 0.50 | ( 0.09, 2.74) | 0.00 | (-0.01,0.01) | |
| Asia | 174 | 3 | 1.7 | 165 | 0 | 0 | 0.1453 | 0.15 | (<0.01, 2.89) | 0.15 | (<0.01, 2.89) | -0.02 | (-0.04,0.01) | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 | ( 0.02, 52.49) | 1.06 | ( 0.02, 54.66) | 0.00 | (-0.04,0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4890 |
| Diabetic | 694 | 12 | 1.7 | 698 | 7 | 1.0 | 0.2430 | 0.58 | ( 0.23, 1.46) | 0.58 | ( 0.23, 1.47) | -0.01 | (-0.02,0.00) | |
| Non-Diabetic | 580 | 5 | 0.9 | 580 | 5 | 0.9 | 1.0000 | 1.00 | ( 0.29, 3.44) | 1.00 | ( 0.29, 3.47) | 0.00 | (-0.01,0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8913 |
| <30 | 889 | 13 | 1.5 | 836 | 9 | 1.1 | 0.4755 | 0.74 | ( 0.32, 1.71) | 0.73 | ( 0.31, 1.72) | 0.00 | (-0.01,0.01) | |
| >=30 | 385 | 4 | 1.0 | 442 | 3 | 0.7 | 0.5727 | 0.65 | ( 0.15, 2.90) | 0.65 | ( 0.14, 2.93) | 0.00 | (-0.02,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1040 |
| <130 | 857 | 12 | 1.4 | 834 | 12 | 1.4 | 0.9465 | 1.03 | ( 0.46, 2.27) | 1.03 | ( 0.46, 2.30) | 0.00 | (-0.01,0.01) | |
| >=130 | 417 | 5 | 1.2 | 444 | 0 | 0 | 0.0335 | 0.09 | (<0.01, 1.54) | 0.08 | (<0.01, 1.53) | -0.01 | (-0.02,0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8588 |
| <75 | 718 | 12 | 1.7 | 678 | 9 | 1.3 | 0.5978 | 0.79 | ( 0.34, 1.87) | 0.79 | ( 0.33, 1.89) | 0.00 | (-0.02,0.01) | |
| 75 to <85 | 348 | 4 | 1.1 | 382 | 3 | 0.8 | 0.6141 | 0.68 | ( 0.15, 3.03) | 0.68 | ( 0.15, 3.06) | 0.00 | (-0.02,0.01) | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | 0.4580 | 0.32 | ( 0.01, 7.77) | 0.32 | ( 0.01, 7.81) | 0.00 | (-0.02,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7599 |
| <30 | 89 | 1 | 1.1 | 115 | 2 | 1.7 | 0.7172 | 1.55 | ( 0.14, 16.80) | 1.56 | ( 0.14, 17.46) | 0.01 | (-0.03,0.04) | |
| 30 to <45 | 348 | 4 | 1.1 | 345 | 3 | 0.9 | 0.7126 | 0.76 | ( 0.17, 3.36) | 0.75 | ( 0.17, 3.40) | 0.00 | (-0.02,0.01) | |
| >=45 | 837 | 12 | 1.4 | 818 | 7 | 0.9 | 0.2698 | 0.60 | ( 0.24, 1.51) | 0.59 | ( 0.23, 1.51) | -0.01 | (-0.02,0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5021 |
| Normal (<30) | 452 | 3 | 0.7 | 456 | 2 | 0.4 | 0.6467 | 0.66 | ( 0.11, 3.94) | 0.66 | ( 0.11, 3.96) | 0.00 | (-0.01,0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 10 | 1.6 | 608 | 9 | 1.5 | 0.8700 | 0.93 | ( 0.38, 2.27) | 0.93 | ( 0.37, 2.30) | 0.00 | (-0.01,0.01) | |
| Macroalbuminuria (>300) | 189 | 4 | 2.1 | 207 | 1 | 0.5 | 0.1460 | 0.23 | ( 0.03, 2.02) | 0.22 | ( 0.02, 2.03) | -0.02 | (-0.04,0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3225 |
| Low, moderate or high | 953 | 13 | 1.4 | 947 | 7 | 0.7 | 0.1820 | 0.54 | ( 0.22, 1.35) | 0.54 | ( 0.21, 1.36) | -0.01 | (-0.02,0.00) | |
| Very high | 315 | 4 | 1.3 | 325 | 5 | 1.5 | 0.7729 | 1.21 | ( 0.33, 4.47) | 1.21 | ( 0.32, 4.57) | 0.00 | (-0.02,0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1851 |
| No | 161 | 2 | 1.2 | 168 | 4 | 2.4 | 0.4403 | 1.92 | ( 0.36, 10.32) | 1.94 | ( 0.35, 10.74) | 0.01 | (-0.02,0.04) | |
| Yes | 1113 | 15 | 1.3 | 1110 | 8 | 0.7 | 0.1441 | 0.53 | ( 0.23, 1.26) | 0.53 | ( 0.22, 1.26) | -0.01 | (-0.01,0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5636 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 | ( 0.01, 6.94) | 0.28 | ( 0.01, 7.07) | -0.02 | (-0.06,0.03) | |
| Yes | 1212 | 16 | 1.3 | 1206 | 12 | 1.0 | 0.4550 | 0.75 | ( 0.36, 1.59) | 0.75 | ( 0.35, 1.59) | 0.00 | (-0.01,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9479 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 | ( 0.02, 40.07) | 0.81 | ( 0.02, 41.54) | 0.00 | (-0.04,0.04) | |
| Yes | 1228 | 17 | 1.4 | 1221 | 12 | 1.0 | 0.3583 | 0.71 | ( 0.34, 1.48) | 0.71 | ( 0.34, 1.49) | 0.00 | (-0.01,0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 47 | 3.7 | 1278 | 38 | 3.0 | 0.3137 | 0.81 | ( 0.53, 1.23) | 0.80 | ( 0.52, 1.24) | -0.01 | (-0.02,0.01) | |
| Sex | | | | | | | | | | | | | | 0.3794 |
| Male | 958 | 37 | 3.9 | 975 | 33 | 3.4 | 0.5741 | 0.88 | ( 0.55, 1.39) | 0.87 | ( 0.54, 1.41) | 0.00 | (-0.02,0.01) | |
| Female | 316 | 10 | 3.2 | 303 | 5 | 1.7 | 0.2206 | 0.52 | ( 0.18, 1.51) | 0.51 | ( 0.17, 1.52) | -0.02 | (-0.04,0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.4034 |
| <65 | 435 | 15 | 3.4 | 392 | 14 | 3.6 | 0.9234 | 1.04 | ( 0.51, 2.12) | 1.04 | ( 0.49, 2.18) | 0.00 | (-0.02,0.03) | |
| >=65 | 839 | 32 | 3.8 | 886 | 24 | 2.7 | 0.1955 | 0.71 | ( 0.42, 1.20) | 0.70 | ( 0.41, 1.20) | -0.01 | (-0.03,0.01) | |
| Region | | | | | | | | | | | | | | 0.8376 |
| North America | 161 | 11 | 6.8 | 159 | 11 | 6.9 | 0.9758 | 1.01 | ( 0.45, 2.27) | 1.01 | ( 0.43, 2.41) | 0.00 | (-0.05,0.06) | |
| Latin America | 420 | 17 | 4.0 | 440 | 12 | 2.7 | 0.2836 | 0.67 | ( 0.33, 1.39) | 0.66 | ( 0.31, 1.41) | -0.01 | (-0.04,0.01) | |
| Europe | 469 | 17 | 3.6 | 467 | 13 | 2.8 | 0.4651 | 0.77 | ( 0.38, 1.56) | 0.76 | ( 0.37, 1.59) | -0.01 | (-0.03,0.01) | |
| Asia | 174 | 1 | 0.6 | 165 | 2 | 1.2 | 0.5311 | 2.11 | ( 0.19, 23.04) | 2.12 | ( 0.19, 23.63) | 0.01 | (-0.01,0.03) | |
| Other | 50 | 1 | 2.0 | 47 | 0 | 0 | 0.5020 | 0.35 | ( 0.01, 8.48) | 0.35 | ( 0.01, 8.74) | -0.02 | (-0.07,0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0617 |
| Diabetic | 694 | 24 | 3.5 | 698 | 27 | 3.9 | 0.6839 | 1.12 | ( 0.65, 1.92) | 1.12 | ( 0.64, 1.97) | 0.00 | (-0.02,0.02) | |
| Non-Diabetic | 580 | 23 | 4.0 | 580 | 11 | 1.9 | 0.0367 | 0.48 | ( 0.24, 0.97) | 0.47 | ( 0.23, 0.97) | -0.02 | (-0.04,0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4261 |
| <30 | 889 | 28 | 3.1 | 836 | 24 | 2.9 | 0.7350 | 0.91 | ( 0.53, 1.56) | 0.91 | ( 0.52, 1.58) | 0.00 | (-0.02,0.01) | |
| >=30 | 385 | 19 | 4.9 | 442 | 14 | 3.2 | 0.1952 | 0.64 | ( 0.33, 1.26) | 0.63 | ( 0.31, 1.27) | -0.02 | (-0.04,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0594 |
| <130 | 857 | 39 | 4.6 | 834 | 24 | 2.9 | 0.0693 | 0.63 | ( 0.38, 1.04) | 0.62 | ( 0.37, 1.04) | -0.02 | (-0.03,0.00) | |
| >=130 | 417 | 8 | 1.9 | 444 | 14 | 3.2 | 0.2512 | 1.64 | ( 0.70, 3.88) | 1.66 | ( 0.69, 4.01) | 0.01 | (-0.01,0.03) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1610 |
| <75 | 718 | 37 | 5.2 | 678 | 22 | 3.2 | 0.0765 | 0.63 | ( 0.38, 1.06) | 0.62 | ( 0.36, 1.06) | -0.02 | (-0.04,0.00) | |
| 75 to <85 | 348 | 6 | 1.7 | 382 | 12 | 3.1 | 0.2175 | 1.82 | ( 0.69, 4.80) | 1.85 | ( 0.69, 4.98) | 0.01 | (-0.01,0.04) | |
| >=85 | 208 | 4 | 1.9 | 218 | 4 | 1.8 | 0.9465 | 0.95 | ( 0.24, 3.77) | 0.95 | ( 0.24, 3.86) | 0.00 | (-0.03,0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0790 |
| <30 | 89 | 6 | 6.7 | 115 | 13 | 11.3 | 0.2661 | 1.68 | ( 0.66, 4.24) | 1.76 | ( 0.64, 4.84) | 0.05 | (-0.03,0.12) | |
| 30 to <45 | 348 | 18 | 5.2 | 345 | 7 | 2.0 | 0.0265 | 0.39 | ( 0.17, 0.93) | 0.38 | ( 0.16, 0.92) | -0.03 | (-0.06,0.00) | |
| >=45 | 837 | 23 | 2.7 | 818 | 18 | 2.2 | 0.4738 | 0.80 | ( 0.44, 1.47) | 0.80 | ( 0.43, 1.49) | -0.01 | (-0.02,0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.0948 |
| Normal (<30) | 452 | 18 | 4.0 | 456 | 10 | 2.2 | 0.1189 | 0.55 | ( 0.26, 1.18) | 0.54 | ( 0.25, 1.18) | -0.02 | (-0.04,0.00) | |
| Microalbuminuria (30 to <=300) | 627 | 23 | 3.7 | 608 | 15 | 2.5 | 0.2217 | 0.67 | ( 0.35, 1.28) | 0.66 | ( 0.34, 1.29) | -0.01 | (-0.03,0.01) | |
| Macroalbuminuria (>300) | 189 | 6 | 3.2 | 207 | 13 | 6.3 | 0.1487 | 1.98 | ( 0.77, 5.10) | 2.04 | ( 0.76, 5.49) | 0.03 | (-0.01,0.07) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2225 |
| Low, moderate or high | 953 | 30 | 3.1 | 947 | 19 | 2.0 | 0.1165 | 0.64 | ( 0.36, 1.12) | 0.63 | ( 0.35, 1.13) | -0.01 | (-0.03,0.00) | |
| Very high | 315 | 17 | 5.4 | 325 | 19 | 5.8 | 0.8052 | 1.08 | ( 0.57, 2.05) | 1.09 | ( 0.56, 2.13) | 0.00 | (-0.03,0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6644 |
| No | 161 | 9 | 5.6 | 168 | 9 | 5.4 | 0.9260 | 0.96 | ( 0.39, 2.35) | 0.96 | ( 0.37, 2.47) | 0.00 | (-0.05,0.05) | |
| Yes | 1113 | 38 | 3.4 | 1110 | 29 | 2.6 | 0.2690 | 0.77 | ( 0.48, 1.23) | 0.76 | ( 0.46, 1.24) | -0.01 | (-0.02,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1370 |
| No | 62 | 4 | 6.5 | 72 | 0 | 0 | 0.0460 | 0.10 | (<0.01, 1.75) | 0.09 | (<0.01, 1.70) | -0.06 | (-0.13,0.00) | |
| Yes | 1212 | 43 | 3.5 | 1206 | 38 | 3.2 | 0.5876 | 0.89 | ( 0.58, 1.36) | 0.88 | ( 0.57, 1.38) | 0.00 | (-0.02,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9986 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 | ( 0.02, 40.07) | 0.81 | ( 0.02, 41.54) | 0.00 | (-0.04,0.04) | |
| Yes | 1228 | 47 | 3.8 | 1221 | 38 | 3.1 | 0.3337 | 0.81 | ( 0.53, 1.24) | 0.81 | ( 0.52, 1.25) | -0.01 | (-0.02,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 5 | 0.4 | 1278 | 1 | 0.1 | 0.1013 | 0.20 | ( 0.02, 1.70) | 0.20 | ( 0.02, 1.70) | 0.00 (-0.01,0.00) | |
| Sex | | | | | | | | | | | | | |
| Male | 958 | 4 | 0.4 | 975 | 1 | 0.1 | | | | | | | |
| Female | 316 | 1 | 0.3 | 303 | 0 | 0 | | | | | | | |
| Age [years] | | | | | | | | | | | | | |
| <65 | 435 | 3 | 0.7 | 392 | 0 | 0 | | | | | | | |
| >=65 | 839 | 2 | 0.2 | 886 | 1 | 0.1 | | | | | | | |
| Region | | | | | | | | | | | | | |
| North America | 161 | 2 | 1.2 | 159 | 1 | 0.6 | | | | | | | |
| Latin America | 420 | 1 | 0.2 | 440 | 0 | 0 | | | | | | | |
| Europe | 469 | 0 | 0 | 467 | 0 | 0 | | | | | | | |
| Asia | 174 | 2 | 1.1 | 165 | 0 | 0 | | | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | |
| Diabetic | 694 | 2 | 0.3 | 698 | 1 | 0.1 | | | | | | | |
| Non-Diabetic | 580 | 3 | 0.5 | 580 | 0 | 0 | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | |
| <30 | 889 | 4 | 0.4 | 836 | 1 | 0.1 | | | | | | | |
| >=30 | 385 | 1 | 0.3 | 442 | 0 | 0 | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | |
| <130 | 857 | 3 | 0.4 | 834 | 1 | 0.1 | | | | | | | |
| >=130 | 417 | 2 | 0.5 | 444 | 0 | 0 | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | |
| <75 | 718 | 3 | 0.4 | 678 | 1 | 0.1 | | | | | | | |
| 75 to <85 | 348 | 0 | 0 | 382 | 0 | 0 | | | | | | | |
| >=85 | 208 | 2 | 1.0 | 218 | 0 | 0 | | | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 1 | 0.9 | | | | | |
| 30 to <45 | 348 | 4 | 1.1 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 1 | 0.1 | 818 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 3 | 0.7 | 456 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 0 | 0 | 608 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 207 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 3 | 0.3 | 947 | 0 | 0 | | | | | |
| Very high | 315 | 2 | 0.6 | 325 | 1 | 0.3 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 1 | 0.6 | 168 | 1 | 0.6 | | | | | |
| Yes | 1113 | 4 | 0.4 | 1110 | 0 | 0 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 4 | 0.3 | 1206 | 1 | 0.1 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 0 | 0 | | | | | |
| Yes | 1228 | 5 | 0.4 | 1221 | 1 | 0.1 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 4 | 0.3 | 1278 | 4 | 0.3 | 0.9965 | 1.00 | ( 0.25, 3.98) | 1.00 | ( 0.25, 3.99) | 0.00 ( 0.00,0.00) | |
| Sex | | | | | | | | | | | | | |
| Male | 958 | 4 | 0.4 | 975 | 3 | 0.3 | | | | | | | |
| Female | 316 | 0 | 0 | 303 | 1 | 0.3 | | | | | | | |
| Age [years] | | | | | | | | | | | | | |
| <65 | 435 | 3 | 0.7 | 392 | 2 | 0.5 | | | | | | | |
| >=65 | 839 | 1 | 0.1 | 886 | 2 | 0.2 | | | | | | | |
| Region | | | | | | | | | | | | | |
| North America | 161 | 1 | 0.6 | 159 | 2 | 1.3 | | | | | | | |
| Latin America | 420 | 2 | 0.5 | 440 | 2 | 0.5 | | | | | | | |
| Europe | 469 | 0 | 0 | 467 | 0 | 0 | | | | | | | |
| Asia | 174 | 1 | 0.6 | 165 | 0 | 0 | | | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | |
| Diabetic | 694 | 4 | 0.6 | 698 | 4 | 0.6 | | | | | | | |
| Non-Diabetic | 580 | 0 | 0 | 580 | 0 | 0 | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | |
| <30 | 889 | 3 | 0.3 | 836 | 1 | 0.1 | | | | | | | |
| >=30 | 385 | 1 | 0.3 | 442 | 3 | 0.7 | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | |
| <130 | 857 | 2 | 0.2 | 834 | 2 | 0.2 | | | | | | | |
| >=130 | 417 | 2 | 0.5 | 444 | 2 | 0.5 | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | |
| <75 | 718 | 2 | 0.3 | 678 | 1 | 0.1 | | | | | | | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 3 | 0.8 | | | | | | | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | | | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 2 | 1.7 | | | | | |
| 30 to <45 | 348 | 2 | 0.6 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 2 | 0.2 | 818 | 2 | 0.2 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 1 | 0.2 | 456 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 1 | 0.2 | 608 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 207 | 3 | 1.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 3 | 0.3 | 947 | 1 | 0.1 | | | | | |
| Very high | 315 | 1 | 0.3 | 325 | 3 | 0.9 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 0 | 0 | 168 | 1 | 0.6 | | | | | |
| Yes | 1113 | 4 | 0.4 | 1110 | 3 | 0.3 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 0 | 0 | 72 | 0 | 0 | | | | | |
| Yes | 1212 | 4 | 0.3 | 1206 | 4 | 0.3 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 0 | 0 | | | | | |
| Yes | 1228 | 4 | 0.3 | 1221 | 4 | 0.3 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 3 | 0.2 | 1278 | 6 | 0.5 | 0.3187 | 1.99 ( 0.50, 7.95) | 2.00 ( 0.50, 8.01) | 0.00 ( 0.00,0.01) | |
| Sex | | | | | | | | | | | |
| Male | 958 | 3 | 0.3 | 975 | 4 | 0.4 | | | | | |
| Female | 316 | 0 | 0 | 303 | 2 | 0.7 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 435 | 1 | 0.2 | 392 | 2 | 0.5 | | | | | |
| >=65 | 839 | 2 | 0.2 | 886 | 4 | 0.5 | | | | | |
| Region | | | | | | | | | | | |
| North America | 161 | 0 | 0 | 159 | 1 | 0.6 | | | | | |
| Latin America | 420 | 1 | 0.2 | 440 | 4 | 0.9 | | | | | |
| Europe | 469 | 2 | 0.4 | 467 | 0 | 0 | | | | | |
| Asia | 174 | 0 | 0 | 165 | 1 | 0.6 | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 2 | 0.3 | 698 | 4 | 0.6 | | | | | |
| Non-Diabetic | 580 | 1 | 0.2 | 580 | 2 | 0.3 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 889 | 2 | 0.2 | 836 | 3 | 0.4 | | | | | |
| >=30 | 385 | 1 | 0.3 | 442 | 3 | 0.7 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 857 | 3 | 0.4 | 834 | 3 | 0.4 | | | | | |
| >=130 | 417 | 0 | 0 | 444 | 3 | 0.7 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 718 | 3 | 0.4 | 678 | 3 | 0.4 | | | | | |
| 75 to <85 | 348 | 0 | 0 | 382 | 2 | 0.5 | | | | | |
| >=85 | 208 | 0 | 0 | 218 | 1 | 0.5 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 0 | 0 | 115 | 1 | 0.9 | | | | | |
| 30 to <45 | 348 | 2 | 0.6 | 345 | 0 | 0 | | | | | |
| >=45 | 837 | 1 | 0.1 | 818 | 5 | 0.6 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 452 | 1 | 0.2 | 456 | 1 | 0.2 | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 2 | 0.3 | 608 | 4 | 0.7 | | | | | |
| Macroalbuminuria (>300) | 189 | 0 | 0 | 207 | 1 | 0.5 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 953 | 1 | 0.1 | 947 | 4 | 0.4 | | | | | |
| Very high | 315 | 2 | 0.6 | 325 | 2 | 0.6 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 161 | 0 | 0 | 168 | 0 | 0 | | | | | |
| Yes | 1113 | 3 | 0.3 | 1110 | 6 | 0.5 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 62 | 1 | 1.6 | 72 | 2 | 2.8 | | | | | |
| Yes | 1212 | 2 | 0.2 | 1206 | 4 | 0.3 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 46 | 0 | 0 | 57 | 0 | 0 | | | | | |
| Yes | 1228 | 3 | 0.2 | 1221 | 6 | 0.5 | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.3.2.4**

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 573 | 45.0 | 1278 | 477 | 37.3 | <0.0001 | 0.83 | ( 0.76, 0.91) | 0.73 | ( 0.62, 0.85) | -0.08 | (-0.11,-0.04) | |
| Sex | | | | | | | | | | | | | | 0.3698 |
| Male | 958 | 439 | 45.8 | 975 | 379 | 38.9 | 0.0020 | 0.85 | ( 0.76, 0.94) | 0.75 | ( 0.63, 0.90) | -0.07 | (-0.11,-0.03) | |
| Female | 316 | 134 | 42.4 | 303 | 98 | 32.3 | 0.0097 | 0.76 | ( 0.62, 0.94) | 0.65 | ( 0.47, 0.90) | -0.10 | (-0.18,-0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.4162 |
| <65 | 435 | 206 | 47.4 | 392 | 146 | 37.2 | 0.0033 | 0.79 | ( 0.67, 0.93) | 0.66 | ( 0.50, 0.87) | -0.10 | (-0.17,-0.03) | |
| >=65 | 839 | 367 | 43.7 | 886 | 331 | 37.4 | 0.0069 | 0.85 | ( 0.76, 0.96) | 0.77 | ( 0.63, 0.93) | -0.06 | (-0.11,-0.02) | |
| Region | | | | | | | | | | | | | | 0.4996 |
| North America | 161 | 84 | 52.2 | 159 | 77 | 48.4 | 0.5028 | 0.93 | ( 0.75, 1.15) | 0.86 | ( 0.56, 1.33) | -0.04 | (-0.15, 0.07) | |
| Latin America | 420 | 169 | 40.2 | 440 | 146 | 33.2 | 0.0318 | 0.82 | ( 0.69, 0.98) | 0.74 | ( 0.56, 0.97) | -0.07 | (-0.13,-0.01) | |
| Europe | 469 | 213 | 45.4 | 467 | 182 | 39.0 | 0.0460 | 0.86 | ( 0.74, <1.00) | 0.77 | ( 0.59, 1.00) | -0.06 | (-0.13, 0.00) | |
| Asia | 174 | 93 | 53.4 | 165 | 61 | 37.0 | 0.0023 | 0.69 | ( 0.54, 0.88) | 0.51 | ( 0.33, 0.79) | -0.16 | (-0.27,-0.06) | |
| Other | 50 | 14 | 28.0 | 47 | 11 | 23.4 | 0.6050 | 0.84 | ( 0.42, 1.65) | 0.79 | ( 0.31, 1.96) | -0.05 | (-0.22, 0.13) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5307 |
| Diabetic | 694 | 315 | 45.4 | 698 | 270 | 38.7 | 0.0113 | 0.85 | ( 0.75, 0.96) | 0.76 | ( 0.61, 0.94) | -0.07 | (-0.12,-0.02) | |
| Non-Diabetic | 580 | 258 | 44.5 | 580 | 207 | 35.7 | 0.0022 | 0.80 | ( 0.70, 0.92) | 0.69 | ( 0.55, 0.88) | -0.09 | (-0.14,-0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4895 |
| <30 | 889 | 396 | 44.5 | 836 | 301 | 36.0 | 0.0003 | 0.81 | ( 0.72, 0.91) | 0.70 | ( 0.58, 0.85) | -0.09 | (-0.13,-0.04) | |
| >=30 | 385 | 177 | 46.0 | 442 | 176 | 39.8 | 0.0743 | 0.87 | ( 0.74, 1.01) | 0.78 | ( 0.59, 1.03) | -0.06 | (-0.13, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7149 |
| <130 | 857 | 406 | 47.4 | 834 | 325 | 39.0 | 0.0005 | 0.82 | ( 0.74, 0.92) | 0.71 | ( 0.58, 0.86) | -0.08 | (-0.13,-0.04) | |
| >=130 | 417 | 167 | 40.0 | 444 | 152 | 34.2 | 0.0775 | 0.85 | ( 0.72, 1.02) | 0.78 | ( 0.59, 1.03) | -0.06 | (-0.12, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0981 |
| <75 | 718 | 325 | 45.3 | 678 | 279 | 41.2 | 0.1210 | 0.91 | ( 0.81, 1.03) | 0.85 | ( 0.68, 1.05) | -0.04 | (-0.09, 0.01) | |
| 75 to <85 | 348 | 153 | 44.0 | 382 | 127 | 33.2 | 0.0029 | 0.76 | ( 0.63, 0.91) | 0.63 | ( 0.47, 0.86) | -0.11 | (-0.18,-0.04) | |
| >=85 | 208 | 95 | 45.7 | 218 | 71 | 32.6 | 0.0056 | 0.71 | ( 0.56, 0.91) | 0.57 | ( 0.39, 0.85) | -0.13 | (-0.22,-0.04) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0694 |
| <30 | 89 | 44 | 49.4 | 115 | 58 | 50.4 | 0.8877 | 1.02 | ( 0.77, 1.35) | 1.04 | ( 0.60, 1.81) | 0.01 | (-0.13, 0.15) | |
| 30 to <45 | 348 | 154 | 44.3 | 345 | 140 | 40.6 | 0.3280 | 0.92 | ( 0.77, 1.09) | 0.86 | ( 0.64, 1.16) | -0.04 | (-0.11, 0.04) | |
| >=45 | 837 | 375 | 44.8 | 818 | 279 | 34.1 | <0.0001 | 0.76 | ( 0.67, 0.86) | 0.64 | ( 0.52, 0.78) | -0.11 | (-0.15,-0.06) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3352 |
| Normal (<30) | 452 | 181 | 40.0 | 456 | 155 | 34.0 | 0.0589 | 0.85 | ( 0.72, 1.01) | 0.77 | ( 0.59, 1.01) | -0.06 | (-0.12, 0.00) | |
| Microalbuminuria (30 to <=300) | 627 | 287 | 45.8 | 608 | 240 | 39.5 | 0.0252 | 0.86 | ( 0.76, 0.98) | 0.77 | ( 0.62, 0.97) | -0.06 | (-0.12,-0.01) | |
| Macroalbuminuria (>300) | 189 | 102 | 54.0 | 207 | 80 | 38.6 | 0.0022 | 0.72 | ( 0.58, 0.89) | 0.54 | ( 0.36, 0.80) | -0.15 | (-0.25,-0.06) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0201 |
| Low, moderate or high | 953 | 419 | 44.0 | 947 | 323 | 34.1 | <0.0001 | 0.78 | ( 0.69, 0.87) | 0.66 | ( 0.55, 0.79) | -0.10 | (-0.14,-0.05) | |
| Very high | 315 | 151 | 47.9 | 325 | 153 | 47.1 | 0.8277 | 0.98 | ( 0.83, 1.16) | 0.97 | ( 0.71, 1.32) | -0.01 | (-0.09, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6135 |
| No | 161 | 74 | 46.0 | 168 | 68 | 40.5 | 0.3152 | 0.88 | ( 0.69, 1.13) | 0.80 | ( 0.52, 1.24) | -0.05 | (-0.16, 0.05) | |
| Yes | 1113 | 499 | 44.8 | 1110 | 409 | 36.8 | 0.0001 | 0.82 | ( 0.74, 0.91) | 0.72 | ( 0.61, 0.85) | -0.08 | (-0.12,-0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9778 |
| No | 62 | 31 | 50.0 | 72 | 30 | 41.7 | 0.3341 | 0.83 | ( 0.58, 1.21) | 0.71 | ( 0.36, 1.42) | -0.08 | (-0.25, 0.09) | |
| Yes | 1212 | 542 | 44.7 | 1206 | 447 | 37.1 | 0.0001 | 0.83 | ( 0.75, 0.91) | 0.73 | ( 0.62, 0.86) | -0.08 | (-0.12,-0.04) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1652 |
| No | 46 | 19 | 41.3 | 57 | 13 | 22.8 | 0.0437 | 0.55 | ( 0.31, 0.99) | 0.42 | ( 0.18, 0.99) | -0.18 | (-0.36,-0.01) | |
| Yes | 1228 | 554 | 45.1 | 1221 | 464 | 38.0 | 0.0004 | 0.84 | ( 0.77, 0.93) | 0.75 | ( 0.63, 0.88) | -0.07 | (-0.11,-0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 424 | 33.3 | 1278 | 412 | 32.2 | 0.5745 | 0.97 | ( 0.87, 1.08) | 0.95 | ( 0.81, 1.13) | -0.01 | (-0.05, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 377 | 29.6 | 1278 | 325 | 25.4 | 0.0186 | 0.86 | ( 0.76, 0.98) | 0.81 | ( 0.68, 0.97) | -0.04 | (-0.08,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.8769 |
| Male | 958 | 284 | 29.6 | 975 | 247 | 25.3 | 0.0337 | 0.85 | ( 0.74, 0.99) | 0.81 | ( 0.66, 0.98) | -0.04 | (-0.08, 0.00) | |
| Female | 316 | 93 | 29.4 | 303 | 78 | 25.7 | 0.3050 | 0.87 | ( 0.68, 1.13) | 0.83 | ( 0.58, 1.18) | -0.04 | (-0.11, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.5444 |
| <65 | 435 | 139 | 32.0 | 392 | 114 | 29.1 | 0.3707 | 0.91 | ( 0.74, 1.12) | 0.87 | ( 0.65, 1.18) | -0.03 | (-0.09, 0.03) | |
| >=65 | 839 | 238 | 28.4 | 886 | 211 | 23.8 | 0.0313 | 0.84 | ( 0.72, 0.98) | 0.79 | ( 0.64, 0.98) | -0.05 | (-0.09, 0.00) | |
| Region | | | | | | | | | | | | | | 0.1008 |
| North America | 161 | 45 | 28.0 | 159 | 51 | 32.1 | 0.4207 | 1.15 | ( 0.82, 1.61) | 1.22 | ( 0.75, 1.97) | 0.04 | (-0.06, 0.14) | |
| Latin America | 420 | 124 | 29.5 | 440 | 94 | 21.4 | 0.0060 | 0.72 | ( 0.57, 0.91) | 0.65 | ( 0.48, 0.88) | -0.08 | (-0.14,-0.02) | |
| Europe | 469 | 115 | 24.5 | 467 | 113 | 24.2 | 0.9083 | 0.99 | ( 0.79, 1.24) | 0.98 | ( 0.73, 1.32) | 0.00 | (-0.06, 0.05) | |
| Asia | 174 | 74 | 42.5 | 165 | 56 | 33.9 | 0.1040 | 0.80 | ( 0.61, 1.05) | 0.69 | ( 0.45, 1.08) | -0.09 | (-0.19, 0.02) | |
| Other | 50 | 19 | 38.0 | 47 | 11 | 23.4 | 0.1201 | 0.62 | ( 0.33, 1.15) | 0.50 | ( 0.21, 1.21) | -0.15 | (-0.33, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9072 |
| Diabetic | 694 | 241 | 34.7 | 698 | 207 | 29.7 | 0.0429 | 0.85 | ( 0.73, <1.00) | 0.79 | ( 0.63, 0.99) | -0.05 | (-0.10, 0.00) | |
| Non-Diabetic | 580 | 136 | 23.4 | 580 | 118 | 20.3 | 0.2013 | 0.87 | ( 0.70, 1.08) | 0.83 | ( 0.63, 1.10) | -0.03 | (-0.08, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9029 |
| <30 | 889 | 260 | 29.2 | 836 | 211 | 25.2 | 0.0619 | 0.86 | ( 0.74, 1.01) | 0.82 | ( 0.66, 1.01) | -0.04 | (-0.08, 0.00) | |
| >=30 | 385 | 117 | 30.4 | 442 | 114 | 25.8 | 0.1416 | 0.85 | ( 0.68, 1.06) | 0.80 | ( 0.59, 1.08) | -0.05 | (-0.11, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5900 |
| <130 | 857 | 245 | 28.6 | 834 | 199 | 23.9 | 0.0272 | 0.83 | ( 0.71, 0.98) | 0.78 | ( 0.63, 0.97) | -0.05 | (-0.09,-0.01) | |
| >=130 | 417 | 132 | 31.7 | 444 | 126 | 28.4 | 0.2943 | 0.90 | ( 0.73, 1.10) | 0.86 | ( 0.64, 1.15) | -0.03 | (-0.09, 0.03) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4121 |
| <75 | 718 | 213 | 29.7 | 678 | 168 | 24.8 | 0.0405 | 0.84 | ( 0.70, 0.99) | 0.78 | ( 0.62, 0.99) | -0.05 | (-0.10, 0.00) | |
| 75 to <85 | 348 | 91 | 26.1 | 382 | 98 | 25.7 | 0.8788 | 0.98 | ( 0.77, 1.25) | 0.97 | ( 0.70, 1.36) | 0.00 | (-0.07, 0.06) | |
| >=85 | 208 | 73 | 35.1 | 218 | 59 | 27.1 | 0.0731 | 0.77 | ( 0.58, 1.03) | 0.69 | ( 0.45, 1.04) | -0.08 | (-0.17, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0869 |
| <30 | 89 | 28 | 31.5 | 115 | 43 | 37.4 | 0.3778 | 1.19 | ( 0.81, 1.75) | 1.30 | ( 0.72, 2.34) | 0.06 | (-0.07, 0.19) | |
| 30 to <45 | 348 | 114 | 32.8 | 345 | 81 | 23.5 | 0.0066 | 0.72 | ( 0.56, 0.91) | 0.63 | ( 0.45, 0.88) | -0.09 | (-0.16,-0.03) | |
| >=45 | 837 | 235 | 28.1 | 818 | 201 | 24.6 | 0.1056 | 0.88 | ( 0.74, 1.03) | 0.83 | ( 0.67, 1.04) | -0.04 | (-0.08, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6353 |
| Normal (<30) | 452 | 113 | 25.0 | 456 | 104 | 22.8 | 0.4385 | 0.91 | ( 0.72, 1.15) | 0.89 | ( 0.65, 1.20) | -0.02 | (-0.08, 0.03) | |
| Microalbuminuria (30 to <=300) | 627 | 194 | 30.9 | 608 | 151 | 24.8 | 0.0168 | 0.80 | ( 0.67, 0.96) | 0.74 | ( 0.57, 0.95) | -0.06 | (-0.11,-0.01) | |
| Macroalbuminuria (>300) | 189 | 70 | 37.0 | 207 | 69 | 33.3 | 0.4405 | 0.90 | ( 0.69, 1.18) | 0.85 | ( 0.56, 1.28) | -0.04 | (-0.13, 0.06) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5050 |
| Low, moderate or high | 953 | 261 | 27.4 | 947 | 228 | 24.1 | 0.0988 | 0.88 | ( 0.75, 1.02) | 0.84 | ( 0.68, 1.03) | -0.03 | (-0.07, 0.01) | |
| Very high | 315 | 116 | 36.8 | 325 | 96 | 29.5 | 0.0502 | 0.80 | ( 0.64, >1.00) | 0.72 | ( 0.52, 1.00) | -0.07 | (-0.15, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6678 |
| No | 161 | 56 | 34.8 | 168 | 47 | 28.0 | 0.1833 | 0.80 | ( 0.58, 1.11) | 0.73 | ( 0.46, 1.16) | -0.07 | (-0.17, 0.03) | |
| Yes | 1113 | 321 | 28.8 | 1110 | 278 | 25.0 | 0.0437 | 0.87 | ( 0.76, <1.00) | 0.82 | ( 0.68, 0.99) | -0.04 | (-0.07, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1852 |
| No | 62 | 19 | 30.6 | 72 | 26 | 36.1 | 0.5041 | 1.18 | ( 0.73, 1.91) | 1.28 | ( 0.62, 2.64) | 0.05 | (-0.10, 0.21) | |
| Yes | 1212 | 358 | 29.5 | 1206 | 299 | 24.8 | 0.0087 | 0.84 | ( 0.74, 0.96) | 0.79 | ( 0.66, 0.94) | -0.05 | (-0.08,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9502 |
| No | 46 | 11 | 23.9 | 57 | 12 | 21.1 | 0.7289 | 0.88 | ( 0.43, 1.81) | 0.85 | ( 0.33, 2.15) | -0.03 | (-0.19, 0.13) | |
| Yes | 1228 | 366 | 29.8 | 1221 | 313 | 25.6 | 0.0212 | 0.86 | ( 0.76, 0.98) | 0.81 | ( 0.68, 0.97) | -0.04 | (-0.08,-0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 252 | 19.8 | 1278 | 248 | 19.4 | 0.8114 | 0.98 | ( 0.84, 1.15) | 0.98 | ( 0.80, 1.19) | 0.00 (-0.03, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 214 | 16.8 | 1278 | 219 | 17.1 | 0.8197 | 1.02 | ( 0.86, 1.21) | 1.02 | ( 0.83, 1.26) | 0.00 (-0.03, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 201 | 15.8 | 1278 | 199 | 15.6 | 0.8863 | 0.99 ( 0.82, 1.18) | 0.98 ( 0.80, 1.22) | 0.00 (-0.03, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 161 | 12.6 | 1278 | 185 | 14.5 | 0.1750 | 1.15 | ( 0.94, 1.39) | 1.17 | ( 0.93, 1.47) | 0.02 (-0.01, 0.04) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 180 | 14.1 | 1278 | 166 | 13.0 | 0.4004 | 0.92 | ( 0.76, 1.12) | 0.91 | ( 0.72, 1.14) | -0.01 (-0.04, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 171 | 13.4 | 1278 | 152 | 11.9 | 0.2455 | 0.89 | ( 0.72, 1.09) | 0.87 | ( 0.69, 1.10) | -0.02 (-0.04, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 163 | 12.8 | 1278 | 138 | 10.8 | 0.1180 | 0.84 ( 0.68, 1.04) | 0.83 ( 0.65, 1.05) | -0.02 (-0.04, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 143 | 11.2 | 1278 | 122 | 9.5 | 0.1646 | 0.85 ( 0.68, 1.07) | 0.83 ( 0.65, 1.08) | -0.02 (-0.04, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 123 | 9.7 | 1278 | 143 | 11.2 | 0.2046 | 1.16 | ( 0.92, 1.46) | 1.18 | ( 0.91, 1.52) | 0.02 (-0.01, 0.04) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 112 | 8.8 | 1278 | 112 | 8.8 | 0.9804 | 1.00 | ( 0.78, 1.28) | 1.00 | ( 0.76, 1.31) | 0.00 | (-0.02, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 93 | 7.3 | 1278 | 76 | 5.9 | 0.1693 | 0.81 | ( 0.61, 1.09) | 0.80 | ( 0.59, 1.10) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 77 | 6.0 | 1278 | 80 | 6.3 | 0.8205 | 1.04 ( 0.76, 1.40) | 1.04 ( 0.75, 1.43) | 0.00 (-0.02, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 60 | 4.7 | 1278 | 50 | 3.9 | 0.3214 | 0.83 ( 0.58, 1.20) | 0.82 ( 0.56, 1.21) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 48 | 3.8 | 1278 | 42 | 3.3 | 0.5099 | 0.87 | ( 0.58, 1.31) | 0.87 | ( 0.57, 1.32) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 41 | 3.2 | 1278 | 46 | 3.6 | 0.5957 | 1.12 | ( 0.74, 1.69) | 1.12 | ( 0.73, 1.72) | 0.00 | (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Endocrine disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 44 | 3.5 | 1278 | 24 | 1.9 | 0.0135 | 0.54 | ( 0.33, 0.89) | 0.54 | ( 0.32, 0.89) | -0.02 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4423 |
| Male | 958 | 36 | 3.8 | 975 | 18 | 1.8 | 0.0108 | 0.49 | ( 0.28, 0.86) | 0.48 | ( 0.27, 0.85) | -0.02 | (-0.03, 0.00) | |
| Female | 316 | 8 | 2.5 | 303 | 6 | 2.0 | 0.6446 | 0.78 | ( 0.27, 2.23) | 0.78 | ( 0.27, 2.27) | -0.01 | (-0.03, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.7546 |
| <65 | 435 | 16 | 3.7 | 392 | 7 | 1.8 | 0.0984 | 0.49 | ( 0.20, 1.17) | 0.48 | ( 0.19, 1.17) | -0.02 | (-0.04, 0.00) | |
| >=65 | 839 | 28 | 3.3 | 886 | 17 | 1.9 | 0.0647 | 0.57 | ( 0.32, 1.04) | 0.57 | ( 0.31, 1.04) | -0.01 | (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | | 0.9478 |
| North America | 161 | 8 | 5.0 | 159 | 4 | 2.5 | 0.2481 | 0.51 | ( 0.16, 1.65) | 0.49 | ( 0.15, 1.67) | -0.02 | (-0.07, 0.02) | |
| Latin America | 420 | 10 | 2.4 | 440 | 7 | 1.6 | 0.4054 | 0.67 | ( 0.26, 1.74) | 0.66 | ( 0.25, 1.76) | -0.01 | (-0.03, 0.01) | |
| Europe | 469 | 15 | 3.2 | 467 | 9 | 1.9 | 0.2186 | 0.60 | ( 0.27, 1.36) | 0.59 | ( 0.26, 1.37) | -0.01 | (-0.03, 0.01) | |
| Asia | 174 | 11 | 6.3 | 165 | 4 | 2.4 | 0.0811 | 0.38 | ( 0.12, 1.18) | 0.37 | ( 0.11, 1.18) | -0.04 | (-0.08, 0.00) | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 | ( 0.02, 52.49) | 1.06 | ( 0.02, 54.66) | 0.00 | (-0.04, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.1237 |
| Diabetic | 694 | 25 | 3.6 | 698 | 9 | 1.3 | 0.0052 | 0.36 | ( 0.17, 0.76) | 0.35 | ( 0.16, 0.75) | -0.02 | (-0.04,-0.01) | |
| Non-Diabetic | 580 | 19 | 3.3 | 580 | 15 | 2.6 | 0.4863 | 0.79 | ( 0.41, 1.54) | 0.78 | ( 0.39, 1.56) | -0.01 | (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1115 |
| <30 | 889 | 34 | 3.8 | 836 | 13 | 1.6 | 0.0038 | 0.41 | ( 0.22, 0.77) | 0.40 | ( 0.21, 0.76) | -0.02 | (-0.04,-0.01) | |
| >=30 | 385 | 10 | 2.6 | 442 | 11 | 2.5 | 0.9210 | 0.96 | ( 0.41, 2.23) | 0.96 | ( 0.40, 2.28) | 0.00 | (-0.02, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7425 |
| <130 | 857 | 34 | 4.0 | 834 | 19 | 2.3 | 0.0463 | 0.57 | ( 0.33, <1.00) | 0.56 | ( 0.32, 1.00) | -0.02 | (-0.03, 0.00) | |
| >=130 | 417 | 10 | 2.4 | 444 | 5 | 1.1 | 0.1540 | 0.47 | ( 0.16, 1.36) | 0.46 | ( 0.16, 1.37) | -0.01 | (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4812 |
| <75 | 718 | 29 | 4.0 | 678 | 15 | 2.2 | 0.0509 | 0.55 | ( 0.30, 1.01) | 0.54 | ( 0.29, 1.01) | -0.02 | (-0.04, 0.00) | |
| 75 to <85 | 348 | 6 | 1.7 | 382 | 6 | 1.6 | 0.8706 | 0.91 | ( 0.30, 2.80) | 0.91 | ( 0.29, 2.85) | 0.00 | (-0.02, 0.02) | |
| >=85 | 208 | 9 | 4.3 | 218 | 3 | 1.4 | 0.0658 | 0.32 | ( 0.09, 1.16) | 0.31 | ( 0.08, 1.16) | -0.03 | (-0.06, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Endocrine disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1293 |
| <30 | 89 | 2 | 2.2 | 115 | 4 | 3.5 | 0.6058 | 1.55 | ( 0.29, 8.26) | 1.57 | ( 0.28, 8.76) | 0.01 | (-0.03, 0.06) | |
| 30 to <45 | 348 | 17 | 4.9 | 345 | 4 | 1.2 | 0.0042 | 0.24 | ( 0.08, 0.70) | 0.23 | ( 0.08, 0.69) | -0.04 | (-0.06,-0.01) | |
| >=45 | 837 | 25 | 3.0 | 818 | 16 | 2.0 | 0.1774 | 0.65 | ( 0.35, 1.22) | 0.65 | ( 0.34, 1.22) | -0.01 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2569 |
| Normal (<30) | 452 | 12 | 2.7 | 456 | 10 | 2.2 | 0.6508 | 0.83 | ( 0.36, 1.89) | 0.82 | ( 0.35, 1.92) | 0.00 | (-0.02, 0.02) | |
| Microalbuminuria (30 to <=300) | 627 | 25 | 4.0 | 608 | 13 | 2.1 | 0.0599 | 0.54 | ( 0.28, 1.04) | 0.53 | ( 0.27, 1.04) | -0.02 | (-0.04, 0.00) | |
| Macroalbuminuria (>300) | 189 | 7 | 3.7 | 207 | 1 | 0.5 | 0.0229 | 0.13 | ( 0.02, 1.05) | 0.13 | ( 0.02, 1.04) | -0.03 | (-0.06, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1648 |
| Low, moderate or high | 953 | 28 | 2.9 | 947 | 19 | 2.0 | 0.1911 | 0.68 | ( 0.38, 1.21) | 0.68 | ( 0.38, 1.22) | -0.01 | (-0.02, 0.00) | |
| Very high | 315 | 16 | 5.1 | 325 | 5 | 1.5 | 0.0119 | 0.30 | ( 0.11, 0.82) | 0.29 | ( 0.11, 0.81) | -0.04 | (-0.06,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5583 |
| No | 161 | 2 | 1.2 | 168 | 2 | 1.2 | 0.9658 | 0.96 | ( 0.14, 6.72) | 0.96 | ( 0.13, 6.88) | 0.00 | (-0.02, 0.02) | |
| Yes | 1113 | 42 | 3.8 | 1110 | 22 | 2.0 | 0.0115 | 0.53 | ( 0.32, 0.87) | 0.52 | ( 0.31, 0.87) | -0.02 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7412 |
| No | 62 | 1 | 1.6 | 72 | 1 | 1.4 | 0.9151 | 0.86 | ( 0.05, 13.48) | 0.86 | ( 0.05, 14.03) | 0.00 | (-0.04, 0.04) | |
| Yes | 1212 | 43 | 3.5 | 1206 | 23 | 1.9 | 0.0133 | 0.54 | ( 0.33, 0.89) | 0.53 | ( 0.32, 0.88) | -0.02 | (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1805 |
| No | 46 | 0 | 0 | 57 | 2 | 3.5 | 0.3207 | 4.05 | ( 0.20, 82.36) | 4.19 | ( 0.20, 89.46) | 0.03 | (-0.03, 0.09) | |
| Yes | 1228 | 44 | 3.6 | 1221 | 22 | 1.8 | 0.0065 | 0.50 | ( 0.30, 0.83) | 0.49 | ( 0.29, 0.83) | -0.02 | (-0.03,-0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Reproductive system and breast disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 37 | 2.9 | 1278 | 43 | 3.4 | 0.5046 | 1.16 ( 0.75, 1.79) | 1.16 ( 0.74, 1.82) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Ear and labyrinth disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 21 | 1.6 | 1278 | 18 | 1.4 | 0.6213 | 0.85 ( 0.46, 1.60) | 0.85 ( 0.45, 1.61) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Product issues

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 8 | 0.6 | 1278 | 15 | 1.2 | 0.1447 | 1.87 | ( 0.80, 4.39) | 1.88 | ( 0.79, 4.45) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 527 | 41.4 | 1278 | 434 | 34.0 | 0.0001 | 0.82 | ( 0.74, 0.91) | 0.73 | ( 0.62, 0.86) | -0.07 | (-0.11,-0.04) | |
| Sex | | | | | | | | | | | | | | 0.5520 |
| Male | 958 | 403 | 42.1 | 975 | 342 | 35.1 | 0.0016 | 0.83 | ( 0.74, 0.93) | 0.74 | ( 0.62, 0.89) | -0.07 | (-0.11,-0.03) | |
| Female | 316 | 124 | 39.2 | 303 | 92 | 30.4 | 0.0205 | 0.77 | ( 0.62, 0.96) | 0.68 | ( 0.48, 0.94) | -0.09 | (-0.16,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3741 |
| <65 | 435 | 194 | 44.6 | 392 | 135 | 34.4 | 0.0029 | 0.77 | ( 0.65, 0.92) | 0.65 | ( 0.49, 0.86) | -0.10 | (-0.17,-0.04) | |
| >=65 | 839 | 333 | 39.7 | 886 | 299 | 33.7 | 0.0105 | 0.85 | ( 0.75, 0.96) | 0.77 | ( 0.64, 0.94) | -0.06 | (-0.10,-0.01) | |
| Region | | | | | | | | | | | | | | 0.3813 |
| North America | 161 | 76 | 47.2 | 159 | 71 | 44.7 | 0.6471 | 0.95 | ( 0.75, 1.20) | 0.90 | ( 0.58, 1.40) | -0.03 | (-0.13, 0.08) | |
| Latin America | 420 | 157 | 37.4 | 440 | 133 | 30.2 | 0.0265 | 0.81 | ( 0.67, 0.98) | 0.73 | ( 0.55, 0.96) | -0.07 | (-0.13,-0.01) | |
| Europe | 469 | 192 | 40.9 | 467 | 164 | 35.1 | 0.0667 | 0.86 | ( 0.73, 1.01) | 0.78 | ( 0.60, 1.02) | -0.06 | (-0.12, 0.00) | |
| Asia | 174 | 90 | 51.7 | 165 | 57 | 34.5 | 0.0014 | 0.67 | ( 0.52, 0.86) | 0.49 | ( 0.32, 0.76) | -0.17 | (-0.28,-0.07) | |
| Other | 50 | 12 | 24.0 | 47 | 9 | 19.1 | 0.5621 | 0.80 | ( 0.37, 1.72) | 0.75 | ( 0.28, 1.99) | -0.05 | (-0.21, 0.11) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5220 |
| Diabetic | 694 | 293 | 42.2 | 698 | 249 | 35.7 | 0.0123 | 0.84 | ( 0.74, 0.96) | 0.76 | ( 0.61, 0.94) | -0.07 | (-0.12,-0.01) | |
| Non-Diabetic | 580 | 234 | 40.3 | 580 | 185 | 31.9 | 0.0027 | 0.79 | ( 0.68, 0.92) | 0.69 | ( 0.54, 0.88) | -0.08 | (-0.14,-0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3679 |
| <30 | 889 | 363 | 40.8 | 836 | 270 | 32.3 | 0.0002 | 0.79 | ( 0.70, 0.90) | 0.69 | ( 0.57, 0.84) | -0.09 | (-0.13,-0.04) | |
| >=30 | 385 | 164 | 42.6 | 442 | 164 | 37.1 | 0.1072 | 0.87 | ( 0.74, 1.03) | 0.79 | ( 0.60, 1.05) | -0.05 | (-0.12, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6592 |
| <130 | 857 | 375 | 43.8 | 834 | 296 | 35.5 | 0.0005 | 0.81 | ( 0.72, 0.91) | 0.71 | ( 0.58, 0.86) | -0.08 | (-0.13,-0.04) | |
| >=130 | 417 | 152 | 36.5 | 444 | 138 | 31.1 | 0.0957 | 0.85 | ( 0.71, 1.03) | 0.79 | ( 0.59, 1.04) | -0.05 | (-0.12, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1233 |
| <75 | 718 | 295 | 41.1 | 678 | 251 | 37.0 | 0.1198 | 0.90 | ( 0.79, 1.03) | 0.84 | ( 0.68, 1.05) | -0.04 | (-0.09, 0.01) | |
| 75 to <85 | 348 | 145 | 41.7 | 382 | 119 | 31.2 | 0.0031 | 0.75 | ( 0.62, 0.91) | 0.63 | ( 0.47, 0.86) | -0.11 | (-0.17,-0.04) | |
| >=85 | 208 | 87 | 41.8 | 218 | 64 | 29.4 | 0.0072 | 0.70 | ( 0.54, 0.91) | 0.58 | ( 0.39, 0.86) | -0.12 | (-0.21,-0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0731 |
| <30 | 89 | 40 | 44.9 | 115 | 55 | 47.8 | 0.6823 | 1.06 ( 0.79, 1.43) | 1.12 ( 0.64, 1.96) | 0.03 (-0.11, 0.17) | |
| 30 to <45 | 348 | 142 | 40.8 | 345 | 125 | 36.2 | 0.2162 | 0.89 ( 0.74, 1.07) | 0.82 ( 0.61, 1.12) | -0.05 (-0.12, 0.03) | |
| >=45 | 837 | 345 | 41.2 | 818 | 254 | 31.1 | <0.0001 | 0.75 ( 0.66, 0.86) | 0.64 ( 0.52, 0.79) | -0.10 (-0.15,-0.06) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.5932 |
| Normal (<30) | 452 | 160 | 35.4 | 456 | 139 | 30.5 | 0.1150 | 0.86 ( 0.71, 1.04) | 0.80 ( 0.61, 1.06) | -0.05 (-0.11, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 268 | 42.7 | 608 | 215 | 35.4 | 0.0079 | 0.83 ( 0.72, 0.95) | 0.73 ( 0.58, 0.92) | -0.07 (-0.13,-0.02) | |
| Macroalbuminuria (>300) | 189 | 96 | 50.8 | 207 | 78 | 37.7 | 0.0086 | 0.74 ( 0.59, 0.93) | 0.59 ( 0.39, 0.87) | -0.13 (-0.23,-0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0307 |
| Low, moderate or high | 953 | 382 | 40.1 | 947 | 291 | 30.7 | <0.0001 | 0.77 ( 0.68, 0.87) | 0.66 ( 0.55, 0.80) | -0.09 (-0.14,-0.05) | |
| Very high | 315 | 142 | 45.1 | 325 | 142 | 43.7 | 0.7240 | 0.97 ( 0.81, 1.15) | 0.95 ( 0.69, 1.29) | -0.01 (-0.09, 0.06) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3286 |
| No | 161 | 66 | 41.0 | 168 | 64 | 38.1 | 0.5909 | 0.93 ( 0.71, 1.21) | 0.89 ( 0.57, 1.38) | -0.03 (-0.13, 0.08) | |
| Yes | 1113 | 461 | 41.4 | 1110 | 370 | 33.3 | <0.0001 | 0.80 ( 0.72, 0.90) | 0.71 ( 0.60, 0.84) | -0.08 (-0.12,-0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6728 |
| No | 62 | 27 | 43.5 | 72 | 28 | 38.9 | 0.5846 | 0.89 ( 0.60, 1.34) | 0.82 ( 0.41, 1.65) | -0.05 (-0.21, 0.12) | |
| Yes | 1212 | 500 | 41.3 | 1206 | 406 | 33.7 | 0.0001 | 0.82 ( 0.74, 0.91) | 0.72 ( 0.61, 0.85) | -0.08 (-0.11,-0.04) | |
| Baseline use of diuretics | | | | | | | | | | | 0.0699 |
| No | 46 | 18 | 39.1 | 57 | 10 | 17.5 | 0.0144 | 0.45 ( 0.23, 0.87) | 0.33 ( 0.13, 0.82) | -0.22 (-0.39,-0.04) | |
| Yes | 1228 | 509 | 41.4 | 1221 | 424 | 34.7 | 0.0006 | 0.84 ( 0.76, 0.93) | 0.75 ( 0.64, 0.89) | -0.07 (-0.11,-0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 136 | 10.7 | 1278 | 144 | 11.3 | 0.6320 | 1.06 ( 0.85, 1.32) | 1.06 ( 0.83, 1.36) | 0.01 (-0.02, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 108 | 8.5 | 1278 | 74 | 5.8 | 0.0084 | 0.68 | ( 0.51, 0.91) | 0.66 | ( 0.49, 0.90) | -0.03 | (-0.05,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.9358 |
| Male | 958 | 83 | 8.7 | 975 | 58 | 5.9 | 0.0217 | 0.69 | ( 0.50, 0.95) | 0.67 | ( 0.47, 0.94) | -0.03 | (-0.05, 0.00) | |
| Female | 316 | 25 | 7.9 | 303 | 16 | 5.3 | 0.1883 | 0.67 | ( 0.36, 1.23) | 0.65 | ( 0.34, 1.24) | -0.03 | (-0.07, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.1327 |
| <65 | 435 | 46 | 10.6 | 392 | 21 | 5.4 | 0.0060 | 0.51 | ( 0.31, 0.83) | 0.48 | ( 0.28, 0.82) | -0.05 | (-0.09,-0.02) | |
| >=65 | 839 | 62 | 7.4 | 886 | 53 | 6.0 | 0.2414 | 0.81 | ( 0.57, 1.15) | 0.80 | ( 0.55, 1.17) | -0.01 | (-0.04, 0.01) | |
| Region | | | | | | | | | | | | | | 0.4089 |
| North America | 161 | 25 | 15.5 | 159 | 21 | 13.2 | 0.5541 | 0.85 | ( 0.50, 1.46) | 0.83 | ( 0.44, 1.55) | -0.02 | (-0.10, 0.05) | |
| Latin America | 420 | 41 | 9.8 | 440 | 22 | 5.0 | 0.0074 | 0.51 | ( 0.31, 0.84) | 0.49 | ( 0.28, 0.83) | -0.05 | (-0.08,-0.01) | |
| Europe | 469 | 36 | 7.7 | 467 | 27 | 5.8 | 0.2475 | 0.75 | ( 0.47, 1.22) | 0.74 | ( 0.44, 1.24) | -0.02 | (-0.05, 0.01) | |
| Asia | 174 | 3 | 1.7 | 165 | 4 | 2.4 | 0.6505 | 1.41 | ( 0.32, 6.19) | 1.42 | ( 0.31, 6.43) | 0.01 | (-0.02, 0.04) | |
| Other | 50 | 3 | 6.0 | 47 | 0 | 0 | 0.1415 | 0.15 | (<0.01, 2.86) | 0.14 | (<0.01, 2.84) | -0.06 | (-0.13, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5163 |
| Diabetic | 694 | 59 | 8.5 | 698 | 44 | 6.3 | 0.1173 | 0.74 | ( 0.51, 1.08) | 0.72 | ( 0.48, 1.09) | -0.02 | (-0.05, 0.01) | |
| Non-Diabetic | 580 | 49 | 8.4 | 580 | 30 | 5.2 | 0.0268 | 0.61 | ( 0.39, 0.95) | 0.59 | ( 0.37, 0.95) | -0.03 | (-0.06, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5670 |
| <30 | 889 | 65 | 7.3 | 836 | 44 | 5.3 | 0.0805 | 0.72 | ( 0.50, 1.04) | 0.70 | ( 0.47, 1.05) | -0.02 | (-0.04, 0.00) | |
| >=30 | 385 | 43 | 11.2 | 442 | 30 | 6.8 | 0.0267 | 0.61 | ( 0.39, 0.95) | 0.58 | ( 0.36, 0.94) | -0.04 | (-0.08, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8724 |
| <130 | 857 | 79 | 9.2 | 834 | 52 | 6.2 | 0.0218 | 0.68 | ( 0.48, 0.95) | 0.65 | ( 0.46, 0.94) | -0.03 | (-0.06, 0.00) | |
| >=130 | 417 | 29 | 7.0 | 444 | 22 | 5.0 | 0.2142 | 0.71 | ( 0.42, 1.22) | 0.70 | ( 0.39, 1.23) | -0.02 | (-0.05, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8618 |
| <75 | 718 | 73 | 10.2 | 678 | 48 | 7.1 | 0.0404 | 0.70 | ( 0.49, 0.99) | 0.67 | ( 0.46, 0.98) | -0.03 | (-0.06, 0.00) | |
| 75 to <85 | 348 | 23 | 6.6 | 382 | 19 | 5.0 | 0.3433 | 0.75 | ( 0.42, 1.36) | 0.74 | ( 0.40, 1.38) | -0.02 | (-0.05, 0.02) | |
| >=85 | 208 | 12 | 5.8 | 218 | 7 | 3.2 | 0.2010 | 0.56 | ( 0.22, 1.39) | 0.54 | ( 0.21, 1.40) | -0.03 | (-0.06, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3070 |
| <30 | 89 | 15 | 16.9 | 115 | 19 | 16.5 | 0.9497 | 0.98 | ( 0.53, 1.82) | 0.98 | ( 0.47, 2.05) | 0.00 | (-0.11, 0.10) | |
| 30 to <45 | 348 | 37 | 10.6 | 345 | 19 | 5.5 | 0.0133 | 0.52 | ( 0.30, 0.88) | 0.49 | ( 0.28, 0.87) | -0.05 | (-0.09,-0.01) | |
| >=45 | 837 | 56 | 6.7 | 818 | 36 | 4.4 | 0.0421 | 0.66 | ( 0.44, 0.99) | 0.64 | ( 0.42, 0.99) | -0.02 | (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2305 |
| Normal (<30) | 452 | 36 | 8.0 | 456 | 25 | 5.5 | 0.1352 | 0.69 | ( 0.42, 1.13) | 0.67 | ( 0.40, 1.14) | -0.02 | (-0.06, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 52 | 8.3 | 608 | 28 | 4.6 | 0.0085 | 0.56 | ( 0.36, 0.87) | 0.53 | ( 0.33, 0.86) | -0.04 | (-0.06,-0.01) | |
| Macroalbuminuria (>300) | 189 | 18 | 9.5 | 207 | 21 | 10.1 | 0.8359 | 1.07 | ( 0.59, 1.94) | 1.07 | ( 0.55, 2.08) | 0.01 | (-0.05, 0.06) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2465 |
| Low, moderate or high | 953 | 67 | 7.0 | 947 | 40 | 4.2 | 0.0080 | 0.60 | ( 0.41, 0.88) | 0.58 | ( 0.39, 0.87) | -0.03 | (-0.05,-0.01) | |
| Very high | 315 | 39 | 12.4 | 325 | 34 | 10.5 | 0.4451 | 0.84 | ( 0.55, 1.30) | 0.83 | ( 0.51, 1.35) | -0.02 | (-0.07, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5965 |
| No | 161 | 14 | 8.7 | 168 | 12 | 7.1 | 0.6018 | 0.82 | ( 0.39, 1.72) | 0.81 | ( 0.36, 1.80) | -0.02 | (-0.07, 0.04) | |
| Yes | 1113 | 94 | 8.4 | 1110 | 62 | 5.6 | 0.0083 | 0.66 | ( 0.49, 0.90) | 0.64 | ( 0.46, 0.89) | -0.03 | (-0.05,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6530 |
| No | 62 | 8 | 12.9 | 72 | 5 | 6.9 | 0.2452 | 0.54 | ( 0.19, 1.56) | 0.50 | ( 0.16, 1.63) | -0.06 | (-0.16, 0.04) | |
| Yes | 1212 | 100 | 8.3 | 1206 | 69 | 5.7 | 0.0147 | 0.69 | ( 0.52, 0.93) | 0.67 | ( 0.49, 0.93) | -0.03 | (-0.05,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.7834 |
| No | 46 | 3 | 6.5 | 57 | 2 | 3.5 | 0.4794 | 0.54 | ( 0.09, 3.09) | 0.52 | ( 0.08, 3.26) | -0.03 | (-0.12, 0.06) | |
| Yes | 1228 | 105 | 8.6 | 1221 | 72 | 5.9 | 0.0112 | 0.69 | ( 0.52, 0.92) | 0.67 | ( 0.49, 0.91) | -0.03 | (-0.05,-0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 57 | 4.5 | 1278 | 82 | 6.4 | 0.0306 | 1.43 | ( 1.03, 1.99) | 1.46 | ( 1.03, 2.07) | 0.02 | ( 0.00, 0.04) | |
| Sex | | | | | | | | | | | | | | 0.1847 |
| Male | 958 | 39 | 4.1 | 975 | 65 | 6.7 | 0.0114 | 1.64 | ( 1.11, 2.41) | 1.68 | ( 1.12, 2.53) | 0.03 | ( 0.01, 0.05) | |
| Female | 316 | 18 | 5.7 | 303 | 17 | 5.6 | 0.9632 | 0.98 | ( 0.52, 1.88) | 0.98 | ( 0.50, 1.95) | 0.00 | (-0.04, 0.04) | |
| Age [years] | | | | | | | | | | | | | | 0.8463 |
| <65 | 435 | 18 | 4.1 | 392 | 22 | 5.6 | 0.3238 | 1.36 | ( 0.74, 2.49) | 1.38 | ( 0.73, 2.61) | 0.01 | (-0.01, 0.04) | |
| >=65 | 839 | 39 | 4.6 | 886 | 60 | 6.8 | 0.0580 | 1.46 | ( 0.98, 2.16) | 1.49 | ( 0.98, 2.26) | 0.02 | ( 0.00, 0.04) | |
| Region | | | | | | | | | | | | | | 0.5112 |
| North America | 161 | 10 | 6.2 | 159 | 14 | 8.8 | 0.3784 | 1.42 | ( 0.65, 3.10) | 1.46 | ( 0.63, 3.39) | 0.03 | (-0.03, 0.08) | |
| Latin America | 420 | 12 | 2.9 | 440 | 29 | 6.6 | 0.0102 | 2.31 | ( 1.19, 4.46) | 2.40 | ( 1.21, 4.77) | 0.04 | ( 0.01, 0.07) | |
| Europe | 469 | 23 | 4.9 | 467 | 24 | 5.1 | 0.8692 | 1.05 | ( 0.60, 1.83) | 1.05 | ( 0.58, 1.89) | 0.00 | (-0.03, 0.03) | |
| Asia | 174 | 11 | 6.3 | 165 | 14 | 8.5 | 0.4463 | 1.34 | ( 0.63, 2.87) | 1.37 | ( 0.61, 3.12) | 0.02 | (-0.03, 0.08) | |
| Other | 50 | 1 | 2.0 | 47 | 1 | 2.1 | 0.9647 | 1.06 | ( 0.07, 16.53) | 1.07 | ( 0.06, 17.53) | 0.00 | (-0.06, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7047 |
| Diabetic | 694 | 33 | 4.8 | 698 | 45 | 6.4 | 0.1700 | 1.36 | ( 0.88, 2.10) | 1.38 | ( 0.87, 2.19) | 0.02 | (-0.01, 0.04) | |
| Non-Diabetic | 580 | 24 | 4.1 | 580 | 37 | 6.4 | 0.0873 | 1.54 | ( 0.93, 2.54) | 1.58 | ( 0.93, 2.67) | 0.02 | ( 0.00, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2672 |
| <30 | 889 | 33 | 3.7 | 836 | 51 | 6.1 | 0.0213 | 1.64 | ( 1.07, 2.52) | 1.69 | ( 1.08, 2.64) | 0.02 | ( 0.00, 0.04) | |
| >=30 | 385 | 24 | 6.2 | 442 | 31 | 7.0 | 0.6535 | 1.13 | ( 0.67, 1.88) | 1.13 | ( 0.65, 1.97) | 0.01 | (-0.03, 0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1522 |
| <130 | 857 | 35 | 4.1 | 834 | 58 | 7.0 | 0.0096 | 1.70 | ( 1.13, 2.56) | 1.76 | ( 1.14, 2.70) | 0.03 | ( 0.01, 0.05) | |
| >=130 | 417 | 22 | 5.3 | 444 | 24 | 5.4 | 0.9326 | 1.02 | ( 0.58, 1.80) | 1.03 | ( 0.57, 1.86) | 0.00 | (-0.03, 0.03) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7100 |
| <75 | 718 | 32 | 4.5 | 678 | 45 | 6.6 | 0.0745 | 1.49 | ( 0.96, 2.31) | 1.52 | ( 0.96, 2.43) | 0.02 | ( 0.00, 0.05) | |
| 75 to <85 | 348 | 17 | 4.9 | 382 | 22 | 5.8 | 0.5999 | 1.18 | ( 0.64, 2.18) | 1.19 | ( 0.62, 2.28) | 0.01 | (-0.02, 0.04) | |
| >=85 | 208 | 8 | 3.8 | 218 | 15 | 6.9 | 0.1660 | 1.79 | ( 0.77, 4.13) | 1.85 | ( 0.77, 4.45) | 0.03 | (-0.01, 0.07) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4111 |
| <30 | 89 | 4 | 4.5 | 115 | 12 | 10.4 | 0.1176 | 2.32 | ( 0.77, 6.96) | 2.48 | ( 0.77, 7.96) | 0.06 | (-0.01, 0.13) | |
| 30 to <45 | 348 | 16 | 4.6 | 345 | 27 | 7.8 | 0.0782 | 1.70 | ( 0.93, 3.10) | 1.76 | ( 0.93, 3.33) | 0.03 | ( 0.00, 0.07) | |
| >=45 | 837 | 37 | 4.4 | 818 | 43 | 5.3 | 0.4278 | 1.19 | ( 0.77, 1.83) | 1.20 | ( 0.76, 1.88) | 0.01 | (-0.01, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8530 |
| Normal (<30) | 452 | 22 | 4.9 | 456 | 29 | 6.4 | 0.3288 | 1.31 | ( 0.76, 2.24) | 1.33 | ( 0.75, 2.35) | 0.01 | (-0.01, 0.04) | |
| Microalbuminuria (30 to <=300) | 627 | 23 | 3.7 | 608 | 36 | 5.9 | 0.0635 | 1.61 | ( 0.97, 2.69) | 1.65 | ( 0.97, 2.82) | 0.02 | ( 0.00, 0.05) | |
| Macroalbuminuria (>300) | 189 | 11 | 5.8 | 207 | 17 | 8.2 | 0.3536 | 1.41 | ( 0.68, 2.93) | 1.45 | ( 0.66, 3.18) | 0.02 | (-0.03, 0.07) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2927 |
| Low, moderate or high | 953 | 40 | 4.2 | 947 | 51 | 5.4 | 0.2253 | 1.28 | ( 0.86, 1.92) | 1.30 | ( 0.85, 1.99) | 0.01 | (-0.01, 0.03) | |
| Very high | 315 | 16 | 5.1 | 325 | 31 | 9.5 | 0.0306 | 1.88 | ( 1.05, 3.36) | 1.97 | ( 1.06, 3.68) | 0.04 | ( 0.00, 0.08) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.0368 |
| No | 161 | 4 | 2.5 | 168 | 17 | 10.1 | 0.0046 | 4.07 | ( 1.40, 11.84) | 4.42 | ( 1.45, 13.43) | 0.08 | ( 0.02, 0.13) | |
| Yes | 1113 | 53 | 4.8 | 1110 | 65 | 5.9 | 0.2500 | 1.23 | ( 0.86, 1.75) | 1.24 | ( 0.86, 1.81) | 0.01 | (-0.01, 0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4470 |
| No | 62 | 2 | 3.2 | 72 | 6 | 8.3 | 0.2134 | 2.58 | ( 0.54, 12.34) | 2.73 | ( 0.53, 14.03) | 0.05 | (-0.03, 0.13) | |
| Yes | 1212 | 55 | 4.5 | 1206 | 76 | 6.3 | 0.0554 | 1.39 | ( 0.99, 1.95) | 1.41 | ( 0.99, 2.02) | 0.02 | ( 0.00, 0.04) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1339 |
| No | 46 | 3 | 6.5 | 57 | 1 | 1.8 | 0.2131 | 0.27 | ( 0.03, 2.50) | 0.26 | ( 0.03, 2.55) | -0.05 | (-0.13, 0.03) | |
| Yes | 1228 | 54 | 4.4 | 1221 | 81 | 6.6 | 0.0153 | 1.51 | ( 1.08, 2.11) | 1.54 | ( 1.08, 2.20) | 0.02 | ( 0.00, 0.04) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 75 | 5.9 | 1278 | 59 | 4.6 | 0.1503 | 0.78 | ( 0.56, 1.09) | 0.77 | ( 0.55, 1.10) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 51 | 4.0 | 1278 | 53 | 4.1 | 0.8541 | 1.04 ( 0.71, 1.51) | 1.04 ( 0.70, 1.54) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 50 | 3.9 | 1278 | 36 | 2.8 | 0.1210 | 0.72 | ( 0.47, 1.09) | 0.71 | ( 0.46, 1.10) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 42 | 3.3 | 1278 | 50 | 3.9 | 0.4042 | 1.19 ( 0.79, 1.78) | 1.19 ( 0.79, 1.81) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 48 | 3.8 | 1278 | 41 | 3.2 | 0.4411 | 0.85 | ( 0.57, 1.28) | 0.85 | ( 0.55, 1.29) | -0.01 | (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 41 | 3.2 | 1278 | 43 | 3.4 | 0.8358 | 1.05 ( 0.69, 1.59) | 1.05 ( 0.68, 1.62) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 39 | 3.1 | 1278 | 33 | 2.6 | 0.4649 | 0.84 | ( 0.53, 1.33) | 0.84 | ( 0.52, 1.34) | 0.00 | (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 29 | 2.3 | 1278 | 17 | 1.3 | 0.0725 | 0.58 ( 0.32, 1.06) | 0.58 ( 0.32, 1.06) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 20 | 1.6 | 1278 | 16 | 1.3 | 0.4959 | 0.80 ( 0.42, 1.53) | 0.79 ( 0.41, 1.54) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 9 | 0.7 | 1278 | 17 | 1.3 | 0.1167 | 1.88 ( 0.84, 4.21) | 1.89 ( 0.84, 4.27) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 265 | 20.8 | 1278 | 225 | 17.6 | 0.0405 | 0.85 ( 0.72, 0.99) | 0.81 ( 0.67, 0.99) | -0.03 (-0.06, 0.00) | |
| Sex | | | | | | | | | | | 0.1463 |
| Male | 958 | 201 | 21.0 | 975 | 184 | 18.9 | 0.2456 | 0.90 ( 0.75, 1.08) | 0.88 ( 0.70, 1.10) | -0.02 (-0.06, 0.01) | |
| Female | 316 | 64 | 20.3 | 303 | 41 | 13.5 | 0.0259 | 0.67 ( 0.47, 0.96) | 0.62 ( 0.40, 0.95) | -0.07 (-0.13,-0.01) | |
| Age [years] | | | | | | | | | | | 0.5027 |
| <65 | 435 | 105 | 24.1 | 392 | 75 | 19.1 | 0.0816 | 0.79 ( 0.61, 1.03) | 0.74 ( 0.53, 1.04) | -0.05 (-0.11, 0.01) | |
| >=65 | 839 | 160 | 19.1 | 886 | 150 | 16.9 | 0.2472 | 0.89 ( 0.73, 1.09) | 0.86 ( 0.68, 1.11) | -0.02 (-0.06, 0.01) | |
| Region | | | | | | | | | | | 0.7416 |
| North America | 161 | 48 | 29.8 | 159 | 48 | 30.2 | 0.9417 | 1.01 ( 0.72, 1.42) | 1.02 ( 0.63, 1.64) | 0.00 (-0.10, 0.10) | |
| Latin America | 420 | 81 | 19.3 | 440 | 74 | 16.8 | 0.3467 | 0.87 ( 0.66, 1.16) | 0.85 ( 0.60, 1.20) | -0.02 (-0.08, 0.03) | |
| Europe | 469 | 87 | 18.6 | 467 | 68 | 14.6 | 0.1007 | 0.78 ( 0.59, 1.05) | 0.75 ( 0.53, 1.06) | -0.04 (-0.09, 0.01) | |
| Asia | 174 | 40 | 23.0 | 165 | 30 | 18.2 | 0.2745 | 0.79 ( 0.52, 1.21) | 0.74 ( 0.44, 1.27) | -0.05 (-0.13, 0.04) | |
| Other | 50 | 9 | 18.0 | 47 | 5 | 10.6 | 0.3025 | 0.59 ( 0.21, 1.64) | 0.54 ( 0.17, 1.76) | -0.07 (-0.21, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.9939 |
| Diabetic | 694 | 154 | 22.2 | 698 | 131 | 18.8 | 0.1136 | 0.85 ( 0.69, 1.04) | 0.81 ( 0.62, 1.05) | -0.03 (-0.08, 0.01) | |
| Non-Diabetic | 580 | 111 | 19.1 | 580 | 94 | 16.2 | 0.1907 | 0.85 ( 0.66, 1.09) | 0.82 ( 0.60, 1.11) | -0.03 (-0.07, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.3327 |
| <30 | 889 | 180 | 20.2 | 836 | 134 | 16.0 | 0.0232 | 0.79 ( 0.65, 0.97) | 0.75 ( 0.59, 0.96) | -0.04 (-0.08,-0.01) | |
| >=30 | 385 | 85 | 22.1 | 442 | 91 | 20.6 | 0.6016 | 0.93 ( 0.72, 1.21) | 0.92 ( 0.66, 1.28) | -0.01 (-0.07, 0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.4300 |
| <130 | 857 | 196 | 22.9 | 834 | 169 | 20.3 | 0.1927 | 0.89 ( 0.74, 1.06) | 0.86 ( 0.68, 1.08) | -0.03 (-0.07, 0.01) | |
| >=130 | 417 | 69 | 16.5 | 444 | 56 | 12.6 | 0.1015 | 0.76 ( 0.55, 1.06) | 0.73 ( 0.50, 1.07) | -0.04 (-0.09, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.0285 |
| <75 | 718 | 151 | 21.0 | 678 | 141 | 20.8 | 0.9144 | 0.99 ( 0.81, 1.21) | 0.99 ( 0.76, 1.28) | 0.00 (-0.05, 0.04) | |
| 75 to <85 | 348 | 69 | 19.8 | 382 | 60 | 15.7 | 0.1449 | 0.79 ( 0.58, 1.08) | 0.75 ( 0.51, 1.10) | -0.04 (-0.10, 0.01) | |
| >=85 | 208 | 45 | 21.6 | 218 | 24 | 11.0 | 0.0029 | 0.51 ( 0.32, 0.80) | 0.45 ( 0.26, 0.77) | -0.11 (-0.18,-0.04) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.6577 |
| <30 | 89 | 21 | 23.6 | 115 | 28 | 24.3 | 0.9007 | 1.03 ( 0.63, | 1.69) | 1.04 ( 0.54, | 1.99) | 0.01 (-0.11, 0.13) | |
| 30 to <45 | 348 | 74 | 21.3 | 345 | 63 | 18.3 | 0.3209 | 0.86 ( 0.64, | 1.16) | 0.83 ( 0.57, | 1.20) | -0.03 (-0.09, 0.03) | |
| >=45 | 837 | 170 | 20.3 | 818 | 134 | 16.4 | 0.0390 | 0.81 ( 0.66, | 0.99) | 0.77 ( 0.60, | 0.99) | -0.04 (-0.08, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.9370 |
| Normal (<30) | 452 | 79 | 17.5 | 456 | 65 | 14.3 | 0.1837 | 0.82 ( 0.60, | 1.10) | 0.78 ( 0.55, | 1.12) | -0.03 (-0.08, 0.02) | |
| Microalbuminuria (30 to <=300) | 627 | 136 | 21.7 | 608 | 115 | 18.9 | 0.2255 | 0.87 ( 0.70, | 1.09) | 0.84 ( 0.64, | 1.11) | -0.03 (-0.07, 0.02) | |
| Macroalbuminuria (>300) | 189 | 48 | 25.4 | 207 | 44 | 21.3 | 0.3298 | 0.84 ( 0.58, | 1.20) | 0.79 ( 0.50, | 1.26) | -0.04 (-0.12, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.2307 |
| Low, moderate or high | 953 | 188 | 19.7 | 947 | 149 | 15.7 | 0.0227 | 0.80 ( 0.66, | 0.97) | 0.76 ( 0.60, | 0.96) | -0.04 (-0.07,-0.01) | |
| Very high | 315 | 75 | 23.8 | 325 | 76 | 23.4 | 0.8993 | 0.98 ( 0.74, | 1.30) | 0.98 ( 0.68, | 1.41) | 0.00 (-0.07, 0.06) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.4464 |
| No | 161 | 33 | 20.5 | 168 | 34 | 20.2 | 0.9535 | 0.99 ( 0.64, | 1.51) | 0.98 ( 0.58, | 1.68) | 0.00 (-0.09, 0.08) | |
| Yes | 1113 | 232 | 20.8 | 1110 | 191 | 17.2 | 0.0289 | 0.83 ( 0.69, | 0.98) | 0.79 ( 0.64, | 0.98) | -0.04 (-0.07, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.8884 |
| No | 62 | 17 | 27.4 | 72 | 16 | 22.2 | 0.4863 | 0.81 ( 0.45, | 1.47) | 0.76 ( 0.34, | 1.66) | -0.05 (-0.20, 0.09) | |
| Yes | 1212 | 248 | 20.5 | 1206 | 209 | 17.3 | 0.0492 | 0.85 ( 0.72, | <1.00) | 0.81 ( 0.66, | 1.00) | -0.03 (-0.06, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.4758 |
| No | 46 | 7 | 15.2 | 57 | 5 | 8.8 | 0.3108 | 0.58 ( 0.20, | 1.70) | 0.54 ( 0.16, | 1.82) | -0.06 (-0.19, 0.06) | |
| Yes | 1228 | 258 | 21.0 | 1221 | 220 | 18.0 | 0.0618 | 0.86 ( 0.73, | 1.01) | 0.83 ( 0.68, | 1.01) | -0.03 (-0.06, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 81 | 6.4 | 1278 | 91 | 7.1 | 0.4423 | 1.12 ( 0.84, 1.50) | 1.13 ( 0.83, 1.54) | 0.01 (-0.01, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 66 | 5.2 | 1278 | 49 | 3.8 | 0.1011 | 0.74 ( 0.52, 1.06) | 0.73 ( 0.50, 1.06) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 54 | 4.2 | 1278 | 45 | 3.5 | 0.3480 | 0.83 ( 0.56, 1.22) | 0.82 ( 0.55, 1.23) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 33 | 2.6 | 1278 | 39 | 3.1 | 0.4816 | 1.18 ( 0.75, 1.86) | 1.18 ( 0.74, 1.89) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 35 | 2.7 | 1278 | 31 | 2.4 | 0.6088 | 0.88 ( 0.55, 1.42) | 0.88 ( 0.54, 1.44) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 29 | 2.3 | 1278 | 25 | 2.0 | 0.5742 | 0.86 ( 0.51, 1.46) | 0.86 ( 0.50, 1.47) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 29 | 2.3 | 1278 | 28 | 2.2 | 0.8840 | 0.96 ( 0.58, 1.61) | 0.96 ( 0.57, 1.63) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 25 | 2.0 | 1278 | 12 | 0.9 | 0.0306 | 0.48 ( 0.24, | 0.95) | 0.47 ( 0.24, | 0.95) | -0.01 (-0.02, | 0.00) | |
| Sex | | | | | | | | | | | | | | 0.9085 |
| Male | 958 | 21 | 2.2 | 975 | 10 | 1.0 | 0.0412 | 0.47 ( 0.22, | 0.99) | 0.46 ( 0.22, | 0.99) | -0.01 (-0.02, | 0.00) | |
| Female | 316 | 4 | 1.3 | 303 | 2 | 0.7 | 0.4419 | 0.52 ( 0.10, | 2.83) | 0.52 ( 0.09, | 2.85) | -0.01 (-0.02, | 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.9439 |
| <65 | 435 | 5 | 1.1 | 392 | 2 | 0.5 | 0.3164 | 0.44 ( 0.09, | 2.27) | 0.44 ( 0.09, | 2.29) | -0.01 (-0.02, | 0.01) | |
| >=65 | 839 | 20 | 2.4 | 886 | 10 | 1.1 | 0.0462 | 0.47 ( 0.22, | 1.01) | 0.47 ( 0.22, | 1.00) | -0.01 (-0.02, | 0.00) | |
| Region | | | | | | | | | | | | | | 0.4715 |
| North America | 161 | 9 | 5.6 | 159 | 2 | 1.3 | 0.0334 | 0.23 ( 0.05, | 1.03) | 0.22 ( 0.05, | 1.01) | -0.04 (-0.08, | 0.00) | |
| Latin America | 420 | 1 | 0.2 | 440 | 3 | 0.7 | 0.3391 | 2.86 ( 0.30, | 27.42) | 2.88 ( 0.30, | 27.76) | 0.00 ( 0.00, | 0.01) | |
| Europe | 469 | 10 | 2.1 | 467 | 5 | 1.1 | 0.1960 | 0.50 ( 0.17, | 1.46) | 0.50 ( 0.17, | 1.46) | -0.01 (-0.03, | 0.01) | |
| Asia | 174 | 5 | 2.9 | 165 | 2 | 1.2 | 0.2823 | 0.42 ( 0.08, | 2.14) | 0.41 ( 0.08, | 2.17) | -0.02 (-0.05, | 0.01) | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 ( 0.02, | 52.49) | 1.06 ( 0.02, | 54.66) | 0.00 (-0.04, | 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8991 |
| Diabetic | 694 | 14 | 2.0 | 698 | 7 | 1.0 | 0.1206 | 0.50 ( 0.20, | 1.22) | 0.49 ( 0.20, | 1.23) | -0.01 (-0.02, | 0.00) | |
| Non-Diabetic | 580 | 11 | 1.9 | 580 | 5 | 0.9 | 0.1309 | 0.45 ( 0.16, | 1.30) | 0.45 ( 0.16, | 1.30) | -0.01 (-0.02, | 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8731 |
| <30 | 889 | 21 | 2.4 | 836 | 10 | 1.2 | 0.0685 | 0.51 ( 0.24, | 1.07) | 0.50 ( 0.23, | 1.07) | -0.01 (-0.02, | 0.00) | |
| >=30 | 385 | 4 | 1.0 | 442 | 2 | 0.5 | 0.3216 | 0.44 ( 0.08, | 2.36) | 0.43 ( 0.08, | 2.38) | -0.01 (-0.02, | 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4328 |
| <130 | 857 | 16 | 1.9 | 834 | 9 | 1.1 | 0.1796 | 0.58 ( 0.26, | 1.30) | 0.57 ( 0.25, | 1.30) | -0.01 (-0.02, | 0.00) | |
| >=130 | 417 | 9 | 2.2 | 444 | 3 | 0.7 | 0.0637 | 0.31 ( 0.09, | 1.15) | 0.31 ( 0.08, | 1.15) | -0.01 (-0.03, | 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5848 |
| <75 | 718 | 18 | 2.5 | 678 | 7 | 1.0 | 0.0379 | 0.41 ( 0.17, | 0.98) | 0.41 ( 0.17, | 0.98) | -0.01 (-0.03, | 0.00) | |
| 75 to <85 | 348 | 4 | 1.1 | 382 | 4 | 1.0 | 0.8945 | 0.91 ( 0.23, | 3.61) | 0.91 ( 0.23, | 3.67) | 0.00 (-0.02, | 0.01) | |
| >=85 | 208 | 3 | 1.4 | 218 | 1 | 0.5 | 0.2927 | 0.32 ( 0.03, | 3.03) | 0.31 ( 0.03, | 3.05) | -0.01 (-0.03, | 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4499 |
| <30 | 89 | 4 | 4.5 | 115 | 0 | 0 | 0.0346 | 0.09 | (<0.01, 1.58) | 0.08 | (<0.01, 1.55) | -0.05 | (-0.09, 0.00) | |
| 30 to <45 | 348 | 3 | 0.9 | 345 | 2 | 0.6 | 0.6606 | 0.67 | ( 0.11, 4.00) | 0.67 | ( 0.11, 4.04) | 0.00 | (-0.02, 0.01) | |
| >=45 | 837 | 18 | 2.2 | 818 | 10 | 1.2 | 0.1433 | 0.57 | ( 0.26, 1.22) | 0.56 | ( 0.26, 1.23) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7241 |
| Normal (<30) | 452 | 8 | 1.8 | 456 | 4 | 0.9 | 0.2389 | 0.50 | ( 0.15, 1.63) | 0.49 | ( 0.15, 1.64) | -0.01 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 12 | 1.9 | 608 | 7 | 1.2 | 0.2764 | 0.60 | ( 0.24, 1.52) | 0.60 | ( 0.23, 1.53) | -0.01 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 189 | 4 | 2.1 | 207 | 1 | 0.5 | 0.1460 | 0.23 | ( 0.03, 2.02) | 0.22 | ( 0.02, 2.03) | -0.02 | (-0.04, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5433 |
| Low, moderate or high | 953 | 18 | 1.9 | 947 | 10 | 1.1 | 0.1320 | 0.56 | ( 0.26, 1.20) | 0.55 | ( 0.25, 1.21) | -0.01 | (-0.02, 0.00) | |
| Very high | 315 | 6 | 1.9 | 325 | 2 | 0.6 | 0.1422 | 0.32 | ( 0.07, 1.59) | 0.32 | ( 0.06, 1.59) | -0.01 | (-0.03, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5466 |
| No | 161 | 4 | 2.5 | 168 | 3 | 1.8 | 0.6606 | 0.72 | ( 0.16, 3.16) | 0.71 | ( 0.16, 3.24) | -0.01 | (-0.04, 0.02) | |
| Yes | 1113 | 21 | 1.9 | 1110 | 9 | 0.8 | 0.0279 | 0.43 | ( 0.20, 0.93) | 0.43 | ( 0.19, 0.93) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3338 |
| No | 62 | 3 | 4.8 | 72 | 0 | 0 | 0.0937 | 0.12 | (<0.01, 2.34) | 0.12 | (<0.01, 2.32) | -0.05 | (-0.11, 0.01) | |
| Yes | 1212 | 22 | 1.8 | 1206 | 12 | 1.0 | 0.0868 | 0.55 | ( 0.27, 1.10) | 0.54 | ( 0.27, 1.10) | -0.01 | (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3049 |
| No | 46 | 0 | 0 | 57 | 1 | 1.8 | 0.5704 | 2.43 | ( 0.10, 58.31) | 2.47 | ( 0.10, 62.05) | 0.02 | (-0.04, 0.07) | |
| Yes | 1228 | 25 | 2.0 | 1221 | 11 | 0.9 | 0.0196 | 0.44 | ( 0.22, 0.90) | 0.44 | ( 0.21, 0.89) | -0.01 | (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 23 | 1.8 | 1278 | 24 | 1.9 | 0.8915 | 1.04 ( 0.59, 1.83) | 1.04 ( 0.58, 1.85) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 23 | 1.8 | 1278 | 22 | 1.7 | 0.8721 | 0.95 ( 0.53, 1.70) | 0.95 ( 0.53, 1.72) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 18 | 1.4 | 1278 | 8 | 0.6 | 0.0478 | 0.44 ( 0.19, 1.02) | 0.44 ( 0.19, 1.01) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.3.2.5**

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 375 | 29.4 | 1278 | 303 | 23.7 | 0.0011 | 0.81 ( 0.71, 0.92) | | 0.75 ( 0.62, 0.89) | | -0.06 (-0.09,-0.02) | |
| Sex | | | | | | | | | | | | | 0.6785 |
| Male | 958 | 285 | 29.7 | 975 | 237 | 24.3 | 0.0071 | 0.82 ( 0.71, 0.95) | | 0.76 ( 0.62, 0.93) | | -0.05 (-0.09,-0.01) | |
| Female | 316 | 90 | 28.5 | 303 | 66 | 21.8 | 0.0550 | 0.76 ( 0.58, 1.01) | | 0.70 ( 0.48, 1.01) | | -0.07 (-0.14, 0.00) | |
| Age [years] | | | | | | | | | | | | | 0.7813 |
| <65 | 435 | 138 | 31.7 | 392 | 98 | 25.0 | 0.0325 | 0.79 ( 0.63, 0.98) | | 0.72 ( 0.53, 0.97) | | -0.07 (-0.13,-0.01) | |
| >=65 | 839 | 237 | 28.2 | 886 | 205 | 23.1 | 0.0151 | 0.82 ( 0.70, 0.96) | | 0.76 ( 0.62, 0.95) | | -0.05 (-0.09,-0.01) | |
| Region | | | | | | | | | | | | | 0.3105 |
| North America | 161 | 31 | 19.3 | 159 | 28 | 17.6 | 0.7045 | 0.91 ( 0.58, 1.45) | | 0.90 ( 0.51, 1.58) | | -0.02 (-0.10, 0.07) | |
| Latin America | 420 | 128 | 30.5 | 440 | 106 | 24.1 | 0.0354 | 0.79 ( 0.63, 0.98) | | 0.72 ( 0.54, 0.98) | | -0.06 (-0.12, 0.00) | |
| Europe | 469 | 143 | 30.5 | 467 | 124 | 26.6 | 0.1822 | 0.87 ( 0.71, 1.07) | | 0.82 ( 0.62, 1.10) | | -0.04 (-0.10, 0.02) | |
| Asia | 174 | 66 | 37.9 | 165 | 37 | 22.4 | 0.0019 | 0.59 ( 0.42, 0.83) | | 0.47 ( 0.29, 0.76) | | -0.16 (-0.25,-0.06) | |
| Other | 50 | 7 | 14.0 | 47 | 8 | 17.0 | 0.6809 | 1.22 ( 0.48, 3.09) | | 1.26 ( 0.42, 3.80) | | 0.03 (-0.11, 0.17) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.4049 |
| Diabetic | 694 | 207 | 29.8 | 698 | 176 | 25.2 | 0.0540 | 0.85 ( 0.71, | >1.00) | 0.79 ( 0.63, 1.00) | | -0.05 (-0.09, 0.00) | |
| Non-Diabetic | 580 | 168 | 29.0 | 580 | 127 | 21.9 | 0.0057 | 0.76 ( 0.62, 0.92) | | 0.69 ( 0.53, 0.90) | | -0.07 (-0.12,-0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.3703 |
| <30 | 889 | 260 | 29.2 | 836 | 188 | 22.5 | 0.0014 | 0.77 ( 0.65, 0.90) | | 0.70 ( 0.56, 0.87) | | -0.07 (-0.11,-0.03) | |
| >=30 | 385 | 115 | 29.9 | 442 | 115 | 26.0 | 0.2175 | 0.87 ( 0.70, 1.08) | | 0.83 ( 0.61, 1.12) | | -0.04 (-0.10, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.7902 |
| <130 | 857 | 264 | 30.8 | 834 | 205 | 24.6 | 0.0043 | 0.80 ( 0.68, 0.93) | | 0.73 ( 0.59, 0.91) | | -0.06 (-0.10,-0.02) | |
| >=130 | 417 | 111 | 26.6 | 444 | 98 | 22.1 | 0.1199 | 0.83 ( 0.65, 1.05) | | 0.78 ( 0.57, 1.07) | | -0.05 (-0.10, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.5010 |
| <75 | 718 | 212 | 29.5 | 678 | 172 | 25.4 | 0.0821 | 0.86 ( 0.72, 1.02) | | 0.81 ( 0.64, 1.03) | | -0.04 (-0.09, 0.01) | |
| 75 to <85 | 348 | 100 | 28.7 | 382 | 85 | 22.3 | 0.0443 | 0.77 ( 0.60, 0.99) | | 0.71 ( 0.51, 0.99) | | -0.06 (-0.13, 0.00) | |
| >=85 | 208 | 63 | 30.3 | 218 | 46 | 21.1 | 0.0298 | 0.70 ( 0.50, 0.97) | | 0.62 ( 0.40, 0.96) | | -0.09 (-0.17,-0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3831 |
| <30 | 89 | 33 | 37.1 | 115 | 41 | 35.7 | 0.8335 | 0.96 ( 0.67, 1.39) | 0.94 ( 0.53, 1.67) | -0.01 (-0.15, 0.12) | |
| 30 to <45 | 348 | 101 | 29.0 | 345 | 86 | 24.9 | 0.2246 | 0.86 ( 0.67, 1.10) | 0.81 ( 0.58, 1.14) | -0.04 (-0.11, 0.03) | |
| >=45 | 837 | 241 | 28.8 | 818 | 176 | 21.5 | 0.0007 | 0.75 ( 0.63, 0.88) | 0.68 ( 0.54, 0.85) | -0.07 (-0.11,-0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.3393 |
| Normal (<30) | 452 | 110 | 24.3 | 456 | 91 | 20.0 | 0.1119 | 0.82 ( 0.64, 1.05) | 0.78 ( 0.57, 1.06) | -0.04 (-0.10, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 186 | 29.7 | 608 | 156 | 25.7 | 0.1156 | 0.86 ( 0.72, 1.04) | 0.82 ( 0.64, 1.05) | -0.04 (-0.09, 0.01) | |
| Macroalbuminuria (>300) | 189 | 76 | 40.2 | 207 | 56 | 27.1 | 0.0055 | 0.67 ( 0.51, 0.89) | 0.55 ( 0.36, 0.84) | -0.13 (-0.22,-0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8373 |
| Low, moderate or high | 953 | 257 | 27.0 | 947 | 205 | 21.6 | 0.0069 | 0.80 ( 0.68, 0.94) | 0.75 ( 0.61, 0.92) | -0.05 (-0.09,-0.01) | |
| Very high | 315 | 115 | 36.5 | 325 | 98 | 30.2 | 0.0881 | 0.83 ( 0.66, 1.03) | 0.75 ( 0.54, 1.04) | -0.06 (-0.14, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.0690 |
| No | 161 | 41 | 25.5 | 168 | 47 | 28.0 | 0.6071 | 1.10 ( 0.77, 1.57) | 1.14 ( 0.70, 1.85) | 0.03 (-0.07, 0.12) | |
| Yes | 1113 | 334 | 30.0 | 1110 | 256 | 23.1 | 0.0002 | 0.77 ( 0.67, 0.88) | 0.70 ( 0.58, 0.85) | -0.07 (-0.11,-0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6613 |
| No | 62 | 17 | 27.4 | 72 | 18 | 25.0 | 0.7506 | 0.91 ( 0.52, 1.61) | 0.88 ( 0.41, 1.91) | -0.02 (-0.17, 0.13) | |
| Yes | 1212 | 358 | 29.5 | 1206 | 285 | 23.6 | 0.0010 | 0.80 ( 0.70, 0.91) | 0.74 ( 0.62, 0.88) | -0.06 (-0.09,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.0517 |
| No | 46 | 10 | 21.7 | 57 | 3 | 5.3 | 0.0123 | 0.24 ( 0.07, 0.83) | 0.20 ( 0.05, 0.78) | -0.16 (-0.30,-0.03) | |
| Yes | 1228 | 365 | 29.7 | 1221 | 300 | 24.6 | 0.0041 | 0.83 ( 0.73, 0.94) | 0.77 ( 0.64, 0.92) | -0.05 (-0.09,-0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 82 | 6.4 | 1278 | 54 | 4.2 | 0.0129 | 0.66 ( 0.47, 0.92) | 0.64 ( 0.45, 0.91) | -0.02 (-0.04, 0.00) | | |
| Sex | | | | | | | | | | | | 0.3383 |
| Male | 958 | 62 | 6.5 | 975 | 45 | 4.6 | 0.0743 | 0.71 ( 0.49, 1.04) | 0.70 ( 0.47, 1.04) | -0.02 (-0.04, 0.00) | | |
| Female | 316 | 20 | 6.3 | 303 | 9 | 3.0 | 0.0481 | 0.47 ( 0.22, 1.01) | 0.45 ( 0.20, 1.01) | -0.03 (-0.07, 0.00) | | |
| Age [years] | | | | | | | | | | | | 0.0984 |
| <65 | 435 | 21 | 4.8 | 392 | 19 | 4.8 | 0.9897 | 1.00 ( 0.55, 1.84) | 1.00 ( 0.53, 1.90) | 0.00 (-0.03, 0.03) | | |
| >=65 | 839 | 61 | 7.3 | 886 | 35 | 4.0 | 0.0026 | 0.54 ( 0.36, 0.81) | 0.52 ( 0.34, 0.80) | -0.03 (-0.05,-0.01) | | |
| Region | | | | | | | | | | | | 0.6337 |
| North America | 161 | 15 | 9.3 | 159 | 13 | 8.2 | 0.7181 | 0.88 ( 0.43, 1.78) | 0.87 ( 0.40, 1.89) | -0.01 (-0.07, 0.05) | | |
| Latin America | 420 | 15 | 3.6 | 440 | 8 | 1.8 | 0.1112 | 0.51 ( 0.22, 1.19) | 0.50 ( 0.21, 1.19) | -0.02 (-0.04, 0.00) | | |
| Europe | 469 | 37 | 7.9 | 467 | 25 | 5.4 | 0.1188 | 0.68 ( 0.42, 1.11) | 0.66 ( 0.39, 1.12) | -0.03 (-0.06, 0.01) | | |
| Asia | 174 | 14 | 8.0 | 165 | 6 | 3.6 | 0.0850 | 0.45 ( 0.18, 1.15) | 0.43 ( 0.16, 1.15) | -0.04 (-0.09, 0.01) | | |
| Other | 50 | 1 | 2.0 | 47 | 2 | 4.3 | 0.5214 | 2.13 ( 0.20, 22.70) | 2.18 ( 0.19, 24.84) | 0.02 (-0.05, 0.09) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.6228 |
| Diabetic | 694 | 42 | 6.1 | 698 | 30 | 4.3 | 0.1396 | 0.71 ( 0.45, 1.12) | 0.70 ( 0.43, 1.13) | -0.02 (-0.04, 0.01) | | |
| Non-Diabetic | 580 | 40 | 6.9 | 580 | 24 | 4.1 | 0.0396 | 0.60 ( 0.37, 0.98) | 0.58 ( 0.35, 0.98) | -0.03 (-0.05, 0.00) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.8766 |
| <30 | 889 | 47 | 5.3 | 836 | 29 | 3.5 | 0.0660 | 0.66 ( 0.42, 1.03) | 0.64 ( 0.40, 1.03) | -0.02 (-0.04, 0.00) | | |
| >=30 | 385 | 35 | 9.1 | 442 | 25 | 5.7 | 0.0575 | 0.62 ( 0.38, 1.02) | 0.60 ( 0.35, 1.02) | -0.03 (-0.07, 0.00) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8466 |
| <130 | 857 | 58 | 6.8 | 834 | 38 | 4.6 | 0.0494 | 0.67 ( 0.45, >1.00) | 0.66 ( 0.43, 1.00) | -0.02 (-0.04, 0.00) | | |
| >=130 | 417 | 24 | 5.8 | 444 | 16 | 3.6 | 0.1338 | 0.63 ( 0.34, 1.16) | 0.61 ( 0.32, 1.17) | -0.02 (-0.05, 0.01) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6606 |
| <75 | 718 | 45 | 6.3 | 678 | 32 | 4.7 | 0.2055 | 0.75 ( 0.48, 1.17) | 0.74 ( 0.46, 1.18) | -0.02 (-0.04, 0.01) | | |
| 75 to <85 | 348 | 25 | 7.2 | 382 | 15 | 3.9 | 0.0534 | 0.55 ( 0.29, 1.02) | 0.53 ( 0.27, 1.02) | -0.03 (-0.07, 0.00) | | |
| >=85 | 208 | 12 | 5.8 | 218 | 7 | 3.2 | 0.2010 | 0.56 ( 0.22, 1.39) | 0.54 ( 0.21, 1.40) | -0.03 (-0.06, 0.01) | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.3298 |
| <30 | 89 | 4 | 4.5 | 115 | 6 | 5.2 | 0.8125 | 1.16 ( 0.34, | 3.99) | 1.17 ( 0.32, | 4.28) | 0.01 (-0.05, 0.07) | |
| 30 to <45 | 348 | 20 | 5.7 | 345 | 17 | 4.9 | 0.6313 | 0.86 ( 0.46, | 1.61) | 0.85 ( 0.44, | 1.65) | -0.01 (-0.04, 0.03) | |
| >=45 | 837 | 58 | 6.9 | 818 | 31 | 3.8 | 0.0046 | 0.55 ( 0.36, | 0.84) | 0.53 ( 0.34, | 0.83) | -0.03 (-0.05,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.8650 |
| Normal (<30) | 452 | 29 | 6.4 | 456 | 19 | 4.2 | 0.1299 | 0.65 ( 0.37, | 1.14) | 0.63 ( 0.35, | 1.15) | -0.02 (-0.05, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 41 | 6.5 | 608 | 28 | 4.6 | 0.1391 | 0.70 ( 0.44, | 1.12) | 0.69 ( 0.42, | 1.13) | -0.02 (-0.04, 0.01) | |
| Macroalbuminuria (>300) | 189 | 12 | 6.3 | 207 | 7 | 3.4 | 0.1676 | 0.53 ( 0.21, | 1.32) | 0.52 ( 0.20, | 1.34) | -0.03 (-0.07, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.2398 |
| Low, moderate or high | 953 | 64 | 6.7 | 947 | 37 | 3.9 | 0.0064 | 0.58 ( 0.39, | 0.86) | 0.56 ( 0.37, | 0.86) | -0.03 (-0.05,-0.01) | |
| Very high | 315 | 18 | 5.7 | 325 | 17 | 5.2 | 0.7880 | 0.92 ( 0.48, | 1.74) | 0.91 ( 0.46, | 1.80) | 0.00 (-0.04, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.8668 |
| No | 161 | 11 | 6.8 | 168 | 7 | 4.2 | 0.2879 | 0.61 ( 0.24, | 1.53) | 0.59 ( 0.22, | 1.57) | -0.03 (-0.08, 0.02) | |
| Yes | 1113 | 71 | 6.4 | 1110 | 47 | 4.2 | 0.0241 | 0.66 ( 0.46, | 0.95) | 0.65 ( 0.44, | 0.95) | -0.02 (-0.04, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.4178 |
| No | 62 | 5 | 8.1 | 72 | 2 | 2.8 | 0.1703 | 0.34 ( 0.07, | 1.71) | 0.33 ( 0.06, | 1.74) | -0.05 (-0.13, 0.02) | |
| Yes | 1212 | 77 | 6.4 | 1206 | 52 | 4.3 | 0.0255 | 0.68 ( 0.48, | 0.96) | 0.66 ( 0.46, | 0.95) | -0.02 (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.2377 |
| No | 46 | 3 | 6.5 | 57 | 0 | 0 | 0.0797 | 0.12 (<0.01, | 2.19) | 0.11 (<0.01, | 2.15) | -0.07 (-0.14, 0.01) | |
| Yes | 1228 | 79 | 6.4 | 1221 | 54 | 4.4 | 0.0281 | 0.69 ( 0.49, | 0.96) | 0.67 ( 0.47, | 0.96) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1274 | 46 | 3.6 | 1278 | 26 | 2.0 | 0.0162 | 0.56 ( 0.35, 0.91) | 0.55 ( 0.34, 0.90) | -0.02 (-0.03, 0.00) | |
| Sex | | | | | | | | | | | 0.1559 |
| Male | 958 | 38 | 4.0 | 975 | 18 | 1.8 | 0.0055 | 0.47 ( 0.27, 0.81) | 0.46 ( 0.26, 0.80) | -0.02 (-0.04,-0.01) | |
| Female | 316 | 8 | 2.5 | 303 | 8 | 2.6 | 0.9322 | 1.04 ( 0.40, 2.74) | 1.04 ( 0.39, 2.82) | 0.00 (-0.02, 0.03) | |
| Age [years] | | | | | | | | | | | 0.4978 |
| <65 | 435 | 14 | 3.2 | 392 | 9 | 2.3 | 0.4205 | 0.71 ( 0.31, 1.63) | 0.71 ( 0.30, 1.65) | -0.01 (-0.03, 0.01) | |
| >=65 | 839 | 32 | 3.8 | 886 | 17 | 1.9 | 0.0179 | 0.50 ( 0.28, 0.90) | 0.49 ( 0.27, 0.90) | -0.02 (-0.03, 0.00) | |
| Region | | | | | | | | | | | 0.4613 |
| North America | 161 | 27 | 16.8 | 159 | 17 | 10.7 | 0.1144 | 0.64 ( 0.36, 1.12) | 0.59 ( 0.31, 1.14) | -0.06 (-0.14, 0.01) | |
| Latin America | 420 | 9 | 2.1 | 440 | 3 | 0.7 | 0.0679 | 0.32 ( 0.09, 1.17) | 0.31 ( 0.08, 1.17) | -0.01 (-0.03, 0.00) | |
| Europe | 469 | 5 | 1.1 | 467 | 6 | 1.3 | 0.7562 | 1.21 ( 0.37, 3.92) | 1.21 ( 0.37, 3.99) | 0.00 (-0.01, 0.02) | |
| Asia | 174 | 4 | 2.3 | 165 | 0 | 0 | 0.0813 | 0.12 (<0.01, 2.16) | 0.11 (<0.01, 2.14) | -0.02 (-0.05, 0.00) | |
| Other | 50 | 1 | 2.0 | 47 | 0 | 0 | 0.5020 | 0.35 ( 0.01, 8.48) | 0.35 ( 0.01, 8.74) | -0.02 (-0.07, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | 0.8888 |
| Diabetic | 694 | 29 | 4.2 | 698 | 16 | 2.3 | 0.0466 | 0.55 ( 0.30, >1.00) | 0.54 ( 0.29, 1.00) | -0.02 (-0.04, 0.00) | |
| Non-Diabetic | 580 | 17 | 2.9 | 580 | 10 | 1.7 | 0.1728 | 0.59 ( 0.27, 1.27) | 0.58 ( 0.26, 1.28) | -0.01 (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.8569 |
| <30 | 889 | 28 | 3.1 | 836 | 14 | 1.7 | 0.0470 | 0.53 ( 0.28, >1.00) | 0.52 ( 0.27, 1.00) | -0.01 (-0.03, 0.00) | |
| >=30 | 385 | 18 | 4.7 | 442 | 12 | 2.7 | 0.1326 | 0.58 ( 0.28, 1.19) | 0.57 ( 0.27, 1.20) | -0.02 (-0.05, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.1625 |
| <130 | 857 | 39 | 4.6 | 834 | 18 | 2.2 | 0.0064 | 0.47 ( 0.27, 0.82) | 0.46 ( 0.26, 0.82) | -0.02 (-0.04,-0.01) | |
| >=130 | 417 | 7 | 1.7 | 444 | 8 | 1.8 | 0.8902 | 1.07 ( 0.39, 2.93) | 1.07 ( 0.39, 2.99) | 0.00 (-0.02, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.2619 |
| <75 | 718 | 23 | 3.2 | 678 | 17 | 2.5 | 0.4360 | 0.78 ( 0.42, 1.45) | 0.78 ( 0.41, 1.47) | -0.01 (-0.02, 0.01) | |
| 75 to <85 | 348 | 13 | 3.7 | 382 | 4 | 1.0 | 0.0161 | 0.28 ( 0.09, 0.85) | 0.27 ( 0.09, 0.84) | -0.03 (-0.05, 0.00) | |
| >=85 | 208 | 10 | 4.8 | 218 | 5 | 2.3 | 0.1593 | 0.48 ( 0.17, 1.37) | 0.46 ( 0.16, 1.38) | -0.03 (-0.06, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.5211 |
| <30 | 89 | 3 | 3.4 | 115 | 1 | 0.9 | 0.2013 | 0.26 ( 0.03, 2.44) | 0.25 ( 0.03, 2.46) | -0.03 (-0.07, 0.02) | |
| 30 to <45 | 348 | 11 | 3.2 | 345 | 9 | 2.6 | 0.6642 | 0.83 ( 0.35, 1.97) | 0.82 ( 0.34, 2.01) | -0.01 (-0.03, 0.02) | |
| >=45 | 837 | 32 | 3.8 | 818 | 16 | 2.0 | 0.0236 | 0.51 ( 0.28, 0.93) | 0.50 ( 0.27, 0.92) | -0.02 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.4290 |
| Normal (<30) | 452 | 7 | 1.5 | 456 | 7 | 1.5 | 0.9867 | 0.99 ( 0.35, 2.80) | 0.99 ( 0.34, 2.85) | 0.00 (-0.02, 0.02) | |
| Microalbuminuria (30 to <=300) | 627 | 32 | 5.1 | 608 | 14 | 2.3 | 0.0094 | 0.45 ( 0.24, 0.84) | 0.44 ( 0.23, 0.83) | -0.03 (-0.05,-0.01) | |
| Macroalbuminuria (>300) | 189 | 7 | 3.7 | 207 | 5 | 2.4 | 0.4551 | 0.65 ( 0.21, 2.02) | 0.64 ( 0.20, 2.06) | -0.01 (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.5673 |
| Low, moderate or high | 953 | 35 | 3.7 | 947 | 18 | 1.9 | 0.0190 | 0.52 ( 0.30, 0.91) | 0.51 ( 0.29, 0.90) | -0.02 (-0.03, 0.00) | |
| Very high | 315 | 11 | 3.5 | 325 | 8 | 2.5 | 0.4425 | 0.70 ( 0.29, 1.73) | 0.70 ( 0.28, 1.76) | -0.01 (-0.04, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.4634 |
| No | 161 | 10 | 6.2 | 168 | 4 | 2.4 | 0.0853 | 0.38 ( 0.12, 1.20) | 0.37 ( 0.11, 1.20) | -0.04 (-0.08, 0.01) | |
| Yes | 1113 | 36 | 3.2 | 1110 | 22 | 2.0 | 0.0640 | 0.61 ( 0.36, 1.03) | 0.60 ( 0.35, 1.04) | -0.01 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.3755 |
| No | 62 | 6 | 9.7 | 72 | 2 | 2.8 | 0.0928 | 0.29 ( 0.06, 1.37) | 0.27 ( 0.05, 1.37) | -0.07 (-0.15, 0.01) | |
| Yes | 1212 | 40 | 3.3 | 1206 | 24 | 2.0 | 0.0448 | 0.60 ( 0.37, 0.99) | 0.59 ( 0.36, 0.99) | -0.01 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.7959 |
| No | 46 | 1 | 2.2 | 57 | 1 | 1.8 | 0.8781 | 0.81 ( 0.05, 12.55) | 0.80 ( 0.05, 13.21) | 0.00 (-0.06, 0.05) | |
| Yes | 1228 | 45 | 3.7 | 1221 | 25 | 2.0 | 0.0163 | 0.56 ( 0.34, 0.91) | 0.55 ( 0.33, 0.90) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 40 | 3.1 | 1278 | 44 | 3.4 | 0.6678 | 1.10 ( 0.72, 1.67) | 1.10 ( 0.71, 1.70) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 27 | 2.1 | 1278 | 20 | 1.6 | 0.2977 | 0.74 ( 0.42, 1.31) | 0.73 ( 0.41, 1.32) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina pectoris

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 26 | 2.0 | 1278 | 16 | 1.3 | 0.1173 | 0.61 ( 0.33, 1.14) | 0.61 ( 0.32, 1.14) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure chronic

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 25 | 2.0 | 1278 | 19 | 1.5 | 0.3560 | 0.76 ( 0.42, 1.37) | 0.75 ( 0.41, 1.38) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial flutter

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 19 | 1.5 | 1278 | 18 | 1.4 | 0.8609 | 0.94 ( 0.50, 1.79) | 0.94 ( 0.49, 1.81) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 16 | 1.3 | 1278 | 15 | 1.2 | 0.8497 | 0.93 ( 0.46, 1.88) | 0.93 ( 0.46, 1.90) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 10 | 0.8 | 1278 | 14 | 1.1 | 0.4164 | 1.40 ( 0.62, 3.13) | 1.40 ( 0.62, 3.16) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 91 | 7.1 | 1278 | 90 | 7.0 | 0.9211 | 0.99 ( 0.74, 1.31) | 0.98 ( 0.73, 1.33) | 0.00 (-0.02, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Nasopharyngitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 69 | 5.4 | 1278 | 66 | 5.2 | 0.7764 | 0.95 ( 0.69, 1.32) | 0.95 ( 0.67, 1.35) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 69 | 5.4 | 1278 | 65 | 5.1 | 0.7087 | 0.94 ( 0.68, 1.31) | 0.94 ( 0.66, 1.33) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Upper respiratory tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 45 | 3.5 | 1278 | 53 | 4.1 | 0.4189 | 1.17 ( 0.80, 1.73) | 1.18 ( 0.79, 1.77) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Bronchitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 50 | 3.9 | 1278 | 38 | 3.0 | 0.1879 | 0.76 ( 0.50, 1.15) | 0.75 ( 0.49, 1.15) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Influenza

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 28 | 2.2 | 1278 | 20 | 1.6 | 0.2393 | 0.71 ( 0.40, 1.26) | 0.71 ( 0.40, 1.26) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Gastroenteritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 19 | 1.5 | 1278 | 8 | 0.6 | 0.0326 | 0.42 ( 0.18, 0.96) | 0.42 ( 0.18, 0.95) | -0.01 (-0.02, 0.00) | | |
| Sex | | | | | | | | | | | | 0.9922 |
| Male | 958 | 14 | 1.5 | 975 | 6 | 0.6 | 0.0661 | 0.42 ( 0.16, 1.09) | 0.42 ( 0.16, 1.09) | -0.01 (-0.02, 0.00) | | |
| Female | 316 | 5 | 1.6 | 303 | 2 | 0.7 | 0.2780 | 0.42 ( 0.08, 2.13) | 0.41 ( 0.08, 2.15) | -0.01 (-0.03, 0.01) | | |
| Age [years] | | | | | | | | | | | | 0.7737 |
| <65 | 435 | 9 | 2.1 | 392 | 3 | 0.8 | 0.1175 | 0.37 ( 0.10, 1.36) | 0.37 ( 0.10, 1.36) | -0.01 (-0.03, 0.00) | | |
| >=65 | 839 | 10 | 1.2 | 886 | 5 | 0.6 | 0.1606 | 0.47 ( 0.16, 1.38) | 0.47 ( 0.16, 1.38) | -0.01 (-0.02, 0.00) | | |
| Region | | | | | | | | | | | | 0.9645 |
| North America | 161 | 2 | 1.2 | 159 | 1 | 0.6 | 0.5692 | 0.51 ( 0.05, 5.53) | 0.50 ( 0.05, 5.61) | -0.01 (-0.03, 0.01) | | |
| Latin America | 420 | 8 | 1.9 | 440 | 3 | 0.7 | 0.1106 | 0.36 ( 0.10, 1.34) | 0.35 ( 0.09, 1.34) | -0.01 (-0.03, 0.00) | | |
| Europe | 469 | 3 | 0.6 | 467 | 2 | 0.4 | 0.6573 | 0.67 ( 0.11, 3.99) | 0.67 ( 0.11, 4.02) | 0.00 (-0.01, 0.01) | | |
| Asia | 174 | 4 | 2.3 | 165 | 2 | 1.2 | 0.4482 | 0.53 ( 0.10, 2.84) | 0.52 ( 0.09, 2.89) | -0.01 (-0.04, 0.02) | | |
| Other | 50 | 2 | 4.0 | 47 | 0 | 0 | 0.2628 | 0.21 ( 0.01, 4.31) | 0.20 (<0.01, 4.37) | -0.04 (-0.10, 0.03) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.5208 |
| Diabetic | 694 | 12 | 1.7 | 698 | 4 | 0.6 | 0.0431 | 0.33 ( 0.11, 1.02) | 0.33 ( 0.11, 1.02) | -0.01 (-0.02, 0.00) | | |
| Non-Diabetic | 580 | 7 | 1.2 | 580 | 4 | 0.7 | 0.3634 | 0.57 ( 0.17, 1.94) | 0.57 ( 0.17, 1.95) | -0.01 (-0.02, 0.01) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.4199 |
| <30 | 889 | 12 | 1.3 | 836 | 6 | 0.7 | 0.1966 | 0.53 ( 0.20, 1.41) | 0.53 ( 0.20, 1.41) | -0.01 (-0.02, 0.00) | | |
| >=30 | 385 | 7 | 1.8 | 442 | 2 | 0.5 | 0.0590 | 0.25 ( 0.05, 1.19) | 0.25 ( 0.05, 1.19) | -0.01 (-0.03, 0.00) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8442 |
| <130 | 857 | 13 | 1.5 | 834 | 5 | 0.6 | 0.0661 | 0.40 ( 0.14, 1.10) | 0.39 ( 0.14, 1.10) | -0.01 (-0.02, 0.00) | | |
| >=130 | 417 | 6 | 1.4 | 444 | 3 | 0.7 | 0.2712 | 0.47 ( 0.12, 1.87) | 0.47 ( 0.12, 1.88) | -0.01 (-0.02, 0.01) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.9779 |
| <75 | 718 | 14 | 1.9 | 678 | 6 | 0.9 | 0.0942 | 0.45 ( 0.18, 1.17) | 0.45 ( 0.17, 1.18) | -0.01 (-0.02, 0.00) | | |
| 75 to <85 | 348 | 4 | 1.1 | 382 | 2 | 0.5 | 0.3496 | 0.46 ( 0.08, 2.47) | 0.45 ( 0.08, 2.49) | -0.01 (-0.02, 0.01) | | |
| >=85 | 208 | 1 | 0.5 | 218 | 0 | 0 | 0.4580 | 0.32 ( 0.01, 7.77) | 0.32 ( 0.01, 7.81) | 0.00 (-0.02, 0.01) | | |

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For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Gastroenteritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.1905 |
| <30 | 89 | 5 | 5.6 | 115 | 0 | 0 | 0.0162 | 0.07 (<0.01, 1.26) | 0.07 (<0.01, 1.22) | -0.06 (-0.11,-0.01) | |
| 30 to <45 | 348 | 5 | 1.4 | 345 | 1 | 0.3 | 0.1032 | 0.20 ( 0.02, 1.72) | 0.20 ( 0.02, 1.72) | -0.01 (-0.03, 0.00) | |
| >=45 | 837 | 9 | 1.1 | 818 | 7 | 0.9 | 0.6482 | 0.80 ( 0.30, 2.13) | 0.79 ( 0.29, 2.14) | 0.00 (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.1364 |
| Normal (<30) | 452 | 9 | 2.0 | 456 | 2 | 0.4 | 0.0325 | 0.22 ( 0.05, 1.01) | 0.22 ( 0.05, 1.01) | -0.02 (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 627 | 8 | 1.3 | 608 | 2 | 0.3 | 0.0634 | 0.26 ( 0.05, 1.21) | 0.26 ( 0.05, 1.21) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 189 | 2 | 1.1 | 207 | 4 | 1.9 | 0.4769 | 1.83 ( 0.34, 9.86) | 1.84 ( 0.33, 10.18) | 0.01 (-0.02, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.2689 |
| Low, moderate or high | 953 | 10 | 1.0 | 947 | 6 | 0.6 | 0.3214 | 0.60 ( 0.22, 1.65) | 0.60 ( 0.22, 1.66) | 0.00 (-0.01, 0.00) | |
| Very high | 315 | 9 | 2.9 | 325 | 2 | 0.6 | 0.0291 | 0.22 ( 0.05, 0.99) | 0.21 ( 0.05, 0.98) | -0.02 (-0.04, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.4165 |
| No | 161 | 5 | 3.1 | 168 | 1 | 0.6 | 0.0889 | 0.19 ( 0.02, 1.62) | 0.19 ( 0.02, 1.62) | -0.03 (-0.05, 0.00) | |
| Yes | 1113 | 14 | 1.3 | 1110 | 7 | 0.6 | 0.1264 | 0.50 ( 0.20, 1.24) | 0.50 ( 0.20, 1.24) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.7932 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 ( 0.01, 6.94) | 0.28 ( 0.01, 7.07) | -0.02 (-0.06, 0.03) | |
| Yes | 1212 | 18 | 1.5 | 1206 | 8 | 0.7 | 0.0501 | 0.45 ( 0.19, 1.02) | 0.44 ( 0.19, 1.02) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.7497 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 ( 0.02, 40.07) | 0.81 ( 0.02, 41.54) | 0.00 (-0.04, 0.04) | |
| Yes | 1228 | 19 | 1.5 | 1221 | 8 | 0.7 | 0.0345 | 0.42 ( 0.19, 0.96) | 0.42 ( 0.18, 0.96) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Cellulitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 10 | 0.8 | 1278 | 17 | 1.3 | 0.1783 | 1.69 ( 0.78, 3.69) | 1.70 ( 0.78, 3.74) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Herpes zoster

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 14 | 1.1 | 1278 | 15 | 1.2 | 0.8585 | 1.07 ( 0.52, 2.20) | 1.07 ( 0.51, 2.22) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Septic shock

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 6 | 0.5 | 1278 | 13 | 1.0 | 0.1085 | 2.16 ( 0.82, 5.66) | 2.17 ( 0.82, 5.73) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperkalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 110 | 8.6 | 1278 | 88 | 6.9 | 0.0988 | 0.80 ( 0.61, | 1.04) | 0.78 ( 0.58, | 1.05) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperuricaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 89 | 7.0 | 1278 | 45 | 3.5 | <0.0001 | 0.50 ( 0.36, | 0.72) | 0.49 ( 0.34, | 0.70) | -0.03 (-0.05,-0.02) | |
| Sex | | | | | | | | | | | | | 0.7992 |
| Male | 958 | 68 | 7.1 | 975 | 34 | 3.5 | 0.0004 | 0.49 ( 0.33, | 0.73) | 0.47 ( 0.31, | 0.72) | -0.04 (-0.06,-0.02) | |
| Female | 316 | 21 | 6.6 | 303 | 11 | 3.6 | 0.0903 | 0.55 ( 0.27, | 1.11) | 0.53 ( 0.25, | 1.12) | -0.03 (-0.06, 0.00) | |
| Age [years] | | | | | | | | | | | | | 0.9942 |
| <65 | 435 | 45 | 10.3 | 392 | 21 | 5.4 | 0.0082 | 0.52 ( 0.31, | 0.85) | 0.49 ( 0.29, | 0.84) | -0.05 (-0.09,-0.01) | |
| >=65 | 839 | 44 | 5.2 | 886 | 24 | 2.7 | 0.0068 | 0.52 ( 0.32, | 0.84) | 0.50 ( 0.30, | 0.83) | -0.03 (-0.04,-0.01) | |
| Region | | | | | | | | | | | | | 0.4681 |
| North America | 161 | 0 | 0 | 159 | 0 | 0 | 0.9950 | 1.01 ( 0.02, | 50.72) | 1.01 ( 0.02, | 51.34) | 0.00 (-0.01, 0.01) | |
| Latin America | 420 | 48 | 11.4 | 440 | 18 | 4.1 | <0.0001 | 0.36 ( 0.21, | 0.61) | 0.33 ( 0.19, | 0.58) | -0.07 (-0.11,-0.04) | |
| Europe | 469 | 21 | 4.5 | 467 | 13 | 2.8 | 0.1661 | 0.62 ( 0.32, | 1.23) | 0.61 ( 0.30, | 1.23) | -0.02 (-0.04, 0.01) | |
| Asia | 174 | 18 | 10.3 | 165 | 12 | 7.3 | 0.3195 | 0.70 ( 0.35, | 1.41) | 0.68 ( 0.32, | 1.46) | -0.03 (-0.09, 0.03) | |
| Other | 50 | 2 | 4.0 | 47 | 2 | 4.3 | 0.9496 | 1.06 ( 0.16, | 7.25) | 1.07 ( 0.14, | 7.90) | 0.00 (-0.08, 0.08) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.9734 |
| Diabetic | 694 | 55 | 7.9 | 698 | 28 | 4.0 | 0.0020 | 0.51 ( 0.33, | 0.79) | 0.49 ( 0.30, | 0.78) | -0.04 (-0.06,-0.01) | |
| Non-Diabetic | 580 | 34 | 5.9 | 580 | 17 | 2.9 | 0.0149 | 0.50 ( 0.28, | 0.88) | 0.48 ( 0.27, | 0.88) | -0.03 (-0.05,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.8603 |
| <30 | 889 | 57 | 6.4 | 836 | 26 | 3.1 | 0.0014 | 0.49 ( 0.31, | 0.76) | 0.47 ( 0.29, | 0.75) | -0.03 (-0.05,-0.01) | |
| >=30 | 385 | 32 | 8.3 | 442 | 19 | 4.3 | 0.0167 | 0.52 ( 0.30, | 0.90) | 0.50 ( 0.28, | 0.89) | -0.04 (-0.07,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.1602 |
| <130 | 857 | 62 | 7.2 | 834 | 25 | 3.0 | <0.0001 | 0.41 ( 0.26, | 0.65) | 0.40 ( 0.25, | 0.64) | -0.04 (-0.06,-0.02) | |
| >=130 | 417 | 27 | 6.5 | 444 | 20 | 4.5 | 0.2034 | 0.70 ( 0.40, | 1.22) | 0.68 ( 0.38, | 1.23) | -0.02 (-0.05, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.5352 |
| <75 | 718 | 51 | 7.1 | 678 | 20 | 2.9 | 0.0004 | 0.42 ( 0.25, | 0.69) | 0.40 ( 0.23, | 0.67) | -0.04 (-0.06,-0.02) | |
| 75 to <85 | 348 | 18 | 5.2 | 382 | 13 | 3.4 | 0.2364 | 0.66 ( 0.33, | 1.32) | 0.65 ( 0.31, | 1.34) | -0.02 (-0.05, 0.01) | |
| >=85 | 208 | 20 | 9.6 | 218 | 12 | 5.5 | 0.1076 | 0.57 ( 0.29, | 1.14) | 0.55 ( 0.26, | 1.15) | -0.04 (-0.09, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperuricaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.7577 |
| <30 | 89 | 5 | 5.6 | 115 | 4 | 3.5 | 0.4605 | 0.62 ( 0.17, | 2.24) | 0.61 ( 0.16, | 2.32) | -0.02 (-0.08, 0.04) | |
| 30 to <45 | 348 | 25 | 7.2 | 345 | 10 | 2.9 | 0.0100 | 0.40 ( 0.20, | 0.83) | 0.39 ( 0.18, | 0.82) | -0.04 (-0.08,-0.01) | |
| >=45 | 837 | 59 | 7.0 | 818 | 31 | 3.8 | 0.0035 | 0.54 ( 0.35, | 0.82) | 0.52 ( 0.33, | 0.81) | -0.03 (-0.05,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.2555 |
| Normal (<30) | 452 | 28 | 6.2 | 456 | 13 | 2.9 | 0.0153 | 0.46 ( 0.24, | 0.88) | 0.44 ( 0.23, | 0.87) | -0.03 (-0.06,-0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 50 | 8.0 | 608 | 20 | 3.3 | 0.0004 | 0.41 ( 0.25, | 0.68) | 0.39 ( 0.23, | 0.67) | -0.05 (-0.07,-0.02) | |
| Macroalbuminuria (>300) | 189 | 11 | 5.8 | 207 | 11 | 5.3 | 0.8262 | 0.91 ( 0.41, | 2.06) | 0.91 ( 0.38, | 2.15) | -0.01 (-0.05, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.0601 |
| Low, moderate or high | 953 | 62 | 6.5 | 947 | 37 | 3.9 | 0.0108 | 0.60 ( 0.40, | 0.89) | 0.58 ( 0.38, | 0.89) | -0.03 (-0.05,-0.01) | |
| Very high | 315 | 27 | 8.6 | 325 | 7 | 2.2 | 0.0003 | 0.25 ( 0.11, | 0.57) | 0.23 ( 0.10, | 0.55) | -0.06 (-0.10,-0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.6316 |
| No | 161 | 12 | 7.5 | 168 | 5 | 3.0 | 0.0667 | 0.40 ( 0.14, | 1.11) | 0.38 ( 0.13, | 1.11) | -0.04 (-0.09, 0.00) | |
| Yes | 1113 | 77 | 6.9 | 1110 | 40 | 3.6 | 0.0005 | 0.52 ( 0.36, | 0.76) | 0.50 ( 0.34, | 0.74) | -0.03 (-0.05,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.0144 |
| No | 62 | 3 | 4.8 | 72 | 8 | 11.1 | 0.1872 | 2.30 ( 0.64, | 8.28) | 2.46 ( 0.62, | 9.71) | 0.06 (-0.03, 0.15) | |
| Yes | 1212 | 86 | 7.1 | 1206 | 37 | 3.1 | <0.0001 | 0.43 ( 0.30, | 0.63) | 0.41 ( 0.28, | 0.61) | -0.04 (-0.06,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.4510 |
| No | 46 | 2 | 4.3 | 57 | 0 | 0 | 0.1728 | 0.16 (<0.01, | 3.29) | 0.15 (<0.01, | 3.31) | -0.04 (-0.11, 0.02) | |
| Yes | 1228 | 87 | 7.1 | 1221 | 45 | 3.7 | 0.0002 | 0.52 ( 0.37, | 0.74) | 0.50 ( 0.35, | 0.73) | -0.03 (-0.05,-0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Gout

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 43 | 3.4 | 1278 | 36 | 2.8 | 0.4155 | 0.83 ( 0.54, 1.29) | 0.83 ( 0.53, 1.30) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 37 | 2.9 | 1278 | 37 | 2.9 | 0.9891 | 1.00 ( 0.64, 1.56) | 1.00 ( 0.63, 1.58) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypoglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 33 | 2.6 | 1278 | 32 | 2.5 | 0.8899 | 0.97 ( 0.60, 1.56) | 0.97 ( 0.59, 1.58) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Type 2 diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 33 | 2.6 | 1278 | 24 | 1.9 | 0.2234 | 0.72 ( 0.43, 1.22) | 0.72 ( 0.42, 1.22) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypokalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 25 | 2.0 | 1278 | 31 | 2.4 | 0.4244 | 1.24 ( 0.73, 2.08) | 1.24 ( 0.73, 2.12) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Dehydration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 18 | 1.4 | 1278 | 20 | 1.6 | 0.7511 | 1.11 ( 0.59, 2.08) | 1.11 ( 0.58, 2.11) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 12 | 0.9 | 1278 | 19 | 1.5 | 0.2091 | 1.58 ( 0.77, | 3.24) | 1.59 ( 0.77, | 3.28) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypertriglyceridaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 16 | 1.3 | 1278 | 8 | 0.6 | 0.0993 | 0.50 ( 0.21, 1.16) | 0.50 ( 0.21, 1.16) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyponatraemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 14 | 1.1 | 1278 | 13 | 1.0 | 0.8402 | 0.93 ( 0.44, 1.96) | 0.92 ( 0.43, 1.98) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal impairment

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 88 | 6.9 | 1278 | 105 | 8.2 | 0.2113 | 1.19 ( 0.91, 1.56) | 1.21 ( 0.90, 1.62) | 0.01 (-0.01, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 54 | 4.2 | 1278 | 39 | 3.1 | 0.1096 | 0.72 ( 0.48, 1.08) | 0.71 ( 0.47, 1.08) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 47 | 3.7 | 1278 | 34 | 2.7 | 0.1383 | 0.72 ( 0.47, 1.11) | 0.71 ( 0.46, 1.12) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Chronic kidney disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 20 | 1.6 | 1278 | 25 | 2.0 | 0.4584 | 1.25 ( 0.70, 2.23) | 1.25 ( 0.69, 2.26) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Haematuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 17 | 1.3 | 1278 | 11 | 0.9 | 0.2508 | 0.65 ( 0.30, 1.37) | 0.64 ( 0.30, 1.38) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Microalbuminuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 7 | 0.5 | 1278 | 16 | 1.3 | 0.0604 | 2.28 ( 0.94, 5.52) | 2.29 ( 0.94, 5.60) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Diarrhoea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 46 | 3.6 | 1278 | 43 | 3.4 | 0.7348 | 0.93 ( 0.62, 1.40) | 0.93 ( 0.61, 1.42) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Constipation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 27 | 2.1 | 1278 | 46 | 3.6 | 0.0249 | 1.70 | ( 1.06, 2.71) | 1.72 | ( 1.07, 2.79) | 0.01 | ( 0.00, 0.03) | |
| Sex | | | | | | | | | | | | | | 0.6312 |
| Male | 958 | 21 | 2.2 | 975 | 34 | 3.5 | 0.0868 | 1.59 | ( 0.93, 2.72) | 1.61 | ( 0.93, 2.80) | 0.01 | ( 0.00, 0.03) | |
| Female | 316 | 6 | 1.9 | 303 | 12 | 4.0 | 0.1270 | 2.09 | ( 0.79, 5.49) | 2.13 | ( 0.79, 5.75) | 0.02 | (-0.01, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.2332 |
| <65 | 435 | 8 | 1.8 | 392 | 7 | 1.8 | 0.9542 | 0.97 | ( 0.36, 2.65) | 0.97 | ( 0.35, 2.70) | 0.00 | (-0.02, 0.02) | |
| >=65 | 839 | 19 | 2.3 | 886 | 39 | 4.4 | 0.0138 | 1.94 | ( 1.13, 3.34) | 1.99 | ( 1.14, 3.47) | 0.02 | ( 0.00, 0.04) | |
| Region | | | | | | | | | | | | | | 0.3625 |
| North America | 161 | 4 | 2.5 | 159 | 6 | 3.8 | 0.5075 | 1.52 | ( 0.44, 5.28) | 1.54 | ( 0.43, 5.56) | 0.01 | (-0.03, 0.05) | |
| Latin America | 420 | 3 | 0.7 | 440 | 6 | 1.4 | 0.3496 | 1.91 | ( 0.48, 7.58) | 1.92 | ( 0.48, 7.73) | 0.01 | (-0.01, 0.02) | |
| Europe | 469 | 7 | 1.5 | 467 | 6 | 1.3 | 0.7860 | 0.86 | ( 0.29, 2.54) | 0.86 | ( 0.29, 2.58) | 0.00 | (-0.02, 0.01) | |
| Asia | 174 | 10 | 5.7 | 165 | 26 | 15.8 | 0.0028 | 2.74 | ( 1.36, 5.51) | 3.07 | ( 1.43, 6.58) | 0.10 | ( 0.03, 0.17) | |
| Other | 50 | 3 | 6.0 | 47 | 2 | 4.3 | 0.6977 | 0.71 | ( 0.12, 4.06) | 0.70 | ( 0.11, 4.36) | -0.02 | (-0.10, 0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8999 |
| Diabetic | 694 | 16 | 2.3 | 698 | 28 | 4.0 | 0.0689 | 1.74 | ( 0.95, 3.19) | 1.77 | ( 0.95, 3.30) | 0.02 | ( 0.00, 0.04) | |
| Non-Diabetic | 580 | 11 | 1.9 | 580 | 18 | 3.1 | 0.1880 | 1.64 | ( 0.78, 3.43) | 1.66 | ( 0.78, 3.54) | 0.01 | (-0.01, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5396 |
| <30 | 889 | 21 | 2.4 | 836 | 37 | 4.4 | 0.0175 | 1.87 | ( 1.11, 3.17) | 1.91 | ( 1.11, 3.30) | 0.02 | ( 0.00, 0.04) | |
| >=30 | 385 | 6 | 1.6 | 442 | 9 | 2.0 | 0.6076 | 1.31 | ( 0.47, 3.64) | 1.31 | ( 0.46, 3.72) | 0.00 | (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8504 |
| <130 | 857 | 17 | 2.0 | 834 | 29 | 3.5 | 0.0591 | 1.75 | ( 0.97, 3.17) | 1.78 | ( 0.97, 3.26) | 0.01 | ( 0.00, 0.03) | |
| >=130 | 417 | 10 | 2.4 | 444 | 17 | 3.8 | 0.2287 | 1.60 | ( 0.74, 3.45) | 1.62 | ( 0.73, 3.58) | 0.01 | (-0.01, 0.04) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2942 |
| <75 | 718 | 14 | 1.9 | 678 | 30 | 4.4 | 0.0082 | 2.27 | ( 1.21, 4.24) | 2.33 | ( 1.22, 4.43) | 0.02 | ( 0.01, 0.04) | |
| 75 to <85 | 348 | 8 | 2.3 | 382 | 8 | 2.1 | 0.8504 | 0.91 | ( 0.35, 2.40) | 0.91 | ( 0.34, 2.45) | 0.00 | (-0.02, 0.02) | |
| >=85 | 208 | 5 | 2.4 | 218 | 8 | 3.7 | 0.4477 | 1.53 | ( 0.51, 4.59) | 1.55 | ( 0.50, 4.81) | 0.01 | (-0.02, 0.05) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Constipation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.2826 |
| <30 | 89 | 2 | 2.2 | 115 | 9 | 7.8 | 0.0802 | 3.48 ( 0.77, 15.72) | 3.69 ( 0.78, 17.54) | 0.06 ( 0.00, 0.11) | |
| 30 to <45 | 348 | 8 | 2.3 | 345 | 7 | 2.0 | 0.8072 | 0.88 ( 0.32, 2.41) | 0.88 ( 0.32, 2.45) | 0.00 (-0.02, 0.02) | |
| >=45 | 837 | 17 | 2.0 | 818 | 30 | 3.7 | 0.0451 | 1.81 (>1.00, 3.25) | 1.84 ( 1.00, 3.36) | 0.02 ( 0.00, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.1378 |
| Normal (<30) | 452 | 8 | 1.8 | 456 | 14 | 3.1 | 0.2026 | 1.73 ( 0.73, 4.09) | 1.76 ( 0.73, 4.23) | 0.01 (-0.01, 0.03) | |
| Microalbuminuria (30 to <=300) | 627 | 11 | 1.8 | 608 | 26 | 4.3 | 0.0093 | 2.44 ( 1.22, 4.89) | 2.50 ( 1.23, 5.11) | 0.03 ( 0.01, 0.04) | |
| Macroalbuminuria (>300) | 189 | 8 | 4.2 | 207 | 6 | 2.9 | 0.4727 | 0.68 ( 0.24, 1.94) | 0.68 ( 0.23, 1.98) | -0.01 (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.9989 |
| Low, moderate or high | 953 | 19 | 2.0 | 947 | 32 | 3.4 | 0.0617 | 1.69 ( 0.97, 2.97) | 1.72 ( 0.97, 3.05) | 0.01 ( 0.00, 0.03) | |
| Very high | 315 | 8 | 2.5 | 325 | 14 | 4.3 | 0.2197 | 1.70 ( 0.72, 3.99) | 1.73 ( 0.71, 4.18) | 0.02 (-0.01, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.6261 |
| No | 161 | 10 | 6.2 | 168 | 15 | 8.9 | 0.3525 | 1.44 ( 0.67, 3.11) | 1.48 ( 0.64, 3.40) | 0.03 (-0.03, 0.08) | |
| Yes | 1113 | 17 | 1.5 | 1110 | 31 | 2.8 | 0.0401 | 1.83 ( 1.02, 3.28) | 1.85 ( 1.02, 3.37) | 0.01 ( 0.00, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.5873 |
| No | 62 | 3 | 4.8 | 72 | 4 | 5.6 | 0.8525 | 1.15 ( 0.27, 4.93) | 1.16 ( 0.25, 5.38) | 0.01 (-0.07, 0.08) | |
| Yes | 1212 | 24 | 2.0 | 1206 | 42 | 3.5 | 0.0234 | 1.76 ( 1.07, 2.89) | 1.79 ( 1.07, 2.97) | 0.02 ( 0.00, 0.03) | |
| Baseline use of diuretics | | | | | | | | | | | 0.5886 |
| No | 46 | 1 | 2.2 | 57 | 1 | 1.8 | 0.8781 | 0.81 ( 0.05, 12.55) | 0.80 ( 0.05, 13.21) | 0.00 (-0.06, 0.05) | |
| Yes | 1228 | 26 | 2.1 | 1221 | 45 | 3.7 | 0.0207 | 1.74 ( 1.08, 2.80) | 1.77 ( 1.08, 2.89) | 0.02 ( 0.00, 0.03) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Nausea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 21 | 1.6 | 1278 | 24 | 1.9 | 0.6595 | 1.14 ( 0.64, 2.04) | 1.14 ( 0.63, 2.06) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Abdominal pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 14 | 1.1 | 1278 | 18 | 1.4 | 0.4823 | 1.28 ( 0.64, | 2.57) | 1.29 ( 0.64, | 2.60) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Vomiting

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 17 | 1.3 | 1278 | 9 | 0.7 | 0.1130 | 0.53 ( 0.24, 1.18) | 0.52 ( 0.23, 1.18) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Dyspepsia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 15 | 1.2 | 1278 | 10 | 0.8 | 0.3112 | 0.66 ( 0.30, 1.47) | 0.66 ( 0.30, 1.48) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Abdominal pain upper

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 11 | 0.9 | 1278 | 13 | 1.0 | 0.6873 | 1.18 ( 0.53, 2.62) | 1.18 ( 0.53, 2.64) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 107 | 8.4 | 1278 | 105 | 8.2 | 0.8671 | 0.98 ( 0.76, 1.27) | 0.98 ( 0.74, 1.29) | 0.00 (-0.02, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypertension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 25 | 2.0 | 1278 | 33 | 2.6 | 0.2935 | 1.32 ( 0.79, 2.20) | 1.32 ( 0.78, 2.24) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Orthostatic hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 10 | 0.8 | 1278 | 15 | 1.2 | 0.3187 | 1.50 ( 0.67, 3.32) | 1.50 ( 0.67, 3.35) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Vascular disorders
Preferred term: Peripheral arterial occlusive disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 12 | 0.9 | 1278 | 13 | 1.0 | 0.8469 | 1.08 ( 0.49, 2.36) | 1.08 ( 0.49, 2.38) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Nervous system disorders
Preferred term: Dizziness

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 38 | 3.0 | 1278 | 46 | 3.6 | 0.3827 | 1.21 ( 0.79, 1.84) | 1.21 ( 0.78, 1.88) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Syncope

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 20 | 1.6 | 1278 | 22 | 1.7 | 0.7635 | 1.10 ( 0.60, 2.00) | 1.10 ( 0.60, 2.02) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Headache

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 12 | 0.9 | 1278 | 21 | 1.6 | 0.1169 | 1.74 ( 0.86, 3.53) | 1.76 ( 0.86, 3.59) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 9 | 0.7 | 1278 | 16 | 1.3 | 0.1618 | 1.77 ( 0.79, 4.00) | 1.78 ( 0.78, 4.05) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Fatigue

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 25 | 2.0 | 1278 | 31 | 2.4 | 0.4244 | 1.24 ( 0.73, 2.08) | 1.24 ( 0.73, 2.12) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 30 | 2.4 | 1278 | 25 | 2.0 | 0.4881 | 0.83 ( 0.49, 1.40) | 0.83 ( 0.48, 1.41) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Oedema peripheral

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 28 | 2.2 | 1278 | 21 | 1.6 | 0.3073 | 0.75 ( 0.43, 1.31) | 0.74 ( 0.42, 1.32) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Non-cardiac chest pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 17 | 1.3 | 1278 | 19 | 1.5 | 0.7442 | 1.11 ( 0.58, 2.13) | 1.12 ( 0.58, 2.16) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Asthenia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 15 | 1.2 | 1278 | 10 | 0.8 | 0.3112 | 0.66 ( 0.30, 1.47) | 0.66 ( 0.30, 1.48) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Sudden cardiac death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 13 | 1.0 | 1278 | 6 | 0.5 | 0.1055 | 0.46 ( 0.18, 1.21) | 0.46 ( 0.17, 1.21) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Cough

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 33 | 2.6 | 1278 | 40 | 3.1 | 0.4135 | 1.21 ( 0.77, | 1.90) | 1.22 ( 0.76, | 1.94) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Dyspnoea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 39 | 3.1 | 1278 | 27 | 2.1 | 0.1312 | 0.69 ( 0.43, 1.12) | 0.68 ( 0.42, 1.12) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Chronic obstructive pulmonary disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 17 | 1.3 | 1278 | 20 | 1.6 | 0.6261 | 1.17 ( 0.62, 2.23) | 1.18 ( 0.61, 2.25) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Epistaxis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 15 | 1.2 | 1278 | 9 | 0.7 | 0.2156 | 0.60 ( 0.26, 1.36) | 0.60 ( 0.26, 1.37) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Arthralgia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 24 | 1.9 | 1278 | 36 | 2.8 | 0.1198 | 1.50 ( 0.90, 2.49) | 1.51 ( 0.90, 2.55) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Back pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 33 | 2.6 | 1278 | 30 | 2.3 | 0.6926 | 0.91 ( 0.56, 1.48) | 0.90 ( 0.55, 1.49) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Osteoarthritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 17 | 1.3 | 1278 | 17 | 1.3 | 0.9927 | 1.00 ( 0.51, 1.94) | 1.00 ( 0.51, 1.96) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Pain in extremity

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 16 | 1.3 | 1278 | 17 | 1.3 | 0.8680 | 1.06 ( 0.54, 2.09) | 1.06 ( 0.53, 2.11) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Glomerular filtration rate decreased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 19 | 1.5 | 1278 | 9 | 0.7 | 0.0563 | 0.47 ( 0.21, 1.04) | 0.47 ( 0.21, 1.04) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood creatinine increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 16 | 1.3 | 1278 | 9 | 0.7 | 0.1571 | 0.56 ( 0.25, 1.26) | 0.56 ( 0.25, 1.27) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 28 | 2.2 | 1278 | 43 | 3.4 | 0.0731 | 1.53 ( 0.96, 2.45) | 1.55 ( 0.96, 2.51) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Contusion

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 14 | 1.1 | 1278 | 18 | 1.4 | 0.4823 | 1.28 ( 0.64, | 2.57) | 1.29 ( 0.64, | 2.60) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Skin laceration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 4 | 0.3 | 1278 | 14 | 1.1 | 0.0183 | 3.49 ( 1.15, 10.57) | 3.52 ( 1.15, 10.71) | 0.01 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | 0.4025 |
| Male | 958 | 4 | 0.4 | 975 | 10 | 1.0 | 0.1149 | 2.46 ( 0.77, 7.81) | 2.47 ( 0.77, 7.91) | 0.01 ( 0.00, 0.01) | |
| Female | 316 | 0 | 0 | 303 | 4 | 1.3 | 0.0653 | 9.38 ( 0.51,173.57) | 9.51 ( 0.51,177.41) | 0.01 ( 0.00, 0.03) | |
| Age [years] | | | | | | | | | | | 0.4996 |
| <65 | 435 | 0 | 0 | 392 | 3 | 0.8 | 0.1074 | 7.77 ( 0.40,149.87) | 7.83 ( 0.40,152.00) | 0.01 ( 0.00, 0.02) | |
| >=65 | 839 | 4 | 0.5 | 886 | 11 | 1.2 | 0.0873 | 2.60 ( 0.83, 8.15) | 2.62 ( 0.83, 8.27) | 0.01 ( 0.00, 0.02) | |
| Region | | | | | | | | | | | 0.5850 |
| North America | 161 | 1 | 0.6 | 159 | 10 | 6.3 | 0.0054 | 10.13 ( 1.31, 78.18) | 10.74 ( 1.36, 84.90) | 0.06 ( 0.02, 0.10) | |
| Latin America | 420 | 0 | 0 | 440 | 0 | 0 | 0.9815 | 0.95 ( 0.02, 48.00) | 0.95 ( 0.02, 48.22) | 0.00 ( 0.00, 0.00) | |
| Europe | 469 | 1 | 0.2 | 467 | 1 | 0.2 | 0.9976 | 1.00 ( 0.06, 16.01) | 1.00 ( 0.06, 16.10) | 0.00 (-0.01, 0.01) | |
| Asia | 174 | 1 | 0.6 | 165 | 2 | 1.2 | 0.5311 | 2.11 ( 0.19, 23.04) | 2.12 ( 0.19, 23.63) | 0.01 (-0.01, 0.03) | |
| Other | 50 | 1 | 2.0 | 47 | 1 | 2.1 | 0.9647 | 1.06 ( 0.07, 16.53) | 1.07 ( 0.06, 17.53) | 0.00 (-0.06, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 694 | 1 | 0.1 | 698 | 8 | 1.1 | | | | | |
| Non-Diabetic | 580 | 3 | 0.5 | 580 | 6 | 1.0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.2922 |
| <30 | 889 | 4 | 0.4 | 836 | 8 | 1.0 | 0.2055 | 2.13 ( 0.64, 7.04) | 2.14 ( 0.64, 7.13) | 0.01 ( 0.00, 0.01) | |
| >=30 | 385 | 0 | 0 | 442 | 6 | 1.4 | 0.0358 | 11.33 ( 0.64,200.42) | 11.48 ( 0.64,204.47) | 0.01 ( 0.00, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.8261 |
| <130 | 857 | 3 | 0.4 | 834 | 11 | 1.3 | 0.0279 | 3.77 ( 1.05, 13.46) | 3.80 ( 1.06, 13.69) | 0.01 ( 0.00, 0.02) | |
| >=130 | 417 | 1 | 0.2 | 444 | 3 | 0.7 | 0.3473 | 2.82 ( 0.29, 26.98) | 2.83 ( 0.29, 27.31) | 0.00 ( 0.00, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.3109 |
| <75 | 718 | 2 | 0.3 | 678 | 12 | 1.8 | 0.0052 | 6.35 ( 1.43, 28.29) | 6.45 ( 1.44, 28.93) | 0.01 ( 0.00, 0.03) | |
| 75 to <85 | 348 | 1 | 0.3 | 382 | 1 | 0.3 | 0.9474 | 0.91 ( 0.06, 14.51) | 0.91 ( 0.06, 14.62) | 0.00 (-0.01, 0.01) | |
| >=85 | 208 | 1 | 0.5 | 218 | 1 | 0.5 | 0.9734 | 0.95 ( 0.06, 15.16) | 0.95 ( 0.06, 15.35) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Skin laceration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 89 | 2 | 2.2 | 115 | 1 | 0.9 | | | | | |
| 30 to <45 | 348 | 1 | 0.3 | 345 | 6 | 1.7 | | | | | |
| >=45 | 837 | 1 | 0.1 | 818 | 7 | 0.9 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.8961 |
| Normal (<30) | 452 | 1 | 0.2 | 456 | 5 | 1.1 | 0.1036 | 4.96 ( 0.58, 42.25) | 5.00 ( 0.58, 42.97) | 0.01 ( 0.00, 0.02) | |
| Microalbuminuria (30 to <=300) | 627 | 3 | 0.5 | 608 | 8 | 1.3 | 0.1174 | 2.75 ( 0.73, 10.32) | 2.77 ( 0.73, 10.50) | 0.01 ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 189 | 0 | 0 | 207 | 1 | 0.5 | 0.5186 | 2.74 ( 0.11, 66.86) | 2.75 ( 0.11, 67.99) | 0.00 (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.1777 |
| Low, moderate or high | 953 | 1 | 0.1 | 947 | 9 | 1.0 | 0.0109 | 9.06 ( 1.15, 71.35) | 9.13 ( 1.15, 72.24) | 0.01 ( 0.00, 0.01) | |
| Very high | 315 | 3 | 1.0 | 325 | 5 | 1.5 | 0.5047 | 1.62 ( 0.39, 6.70) | 1.63 ( 0.39, 6.86) | 0.01 (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.7683 |
| No | 161 | 2 | 1.2 | 168 | 6 | 3.6 | 0.1703 | 2.88 ( 0.59, 14.04) | 2.94 ( 0.59, 14.81) | 0.02 (-0.01, 0.06) | |
| Yes | 1113 | 2 | 0.2 | 1110 | 8 | 0.7 | 0.0567 | 4.01 ( 0.85, 18.85) | 4.03 ( 0.85, 19.03) | 0.01 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.4976 |
| No | 62 | 0 | 0 | 72 | 0 | 0 | 0.9410 | 0.86 ( 0.02, 42.87) | 0.86 ( 0.02, 44.08) | 0.00 (-0.03, 0.03) | |
| Yes | 1212 | 4 | 0.3 | 1206 | 14 | 1.2 | 0.0175 | 3.52 ( 1.16, 10.66) | 3.55 ( 1.16, 10.81) | 0.01 ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.4778 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 ( 0.02, 40.07) | 0.81 ( 0.02, 41.54) | 0.00 (-0.04, 0.04) | |
| Yes | 1228 | 4 | 0.3 | 1221 | 14 | 1.1 | 0.0174 | 3.52 ( 1.16, 10.66) | 3.55 ( 1.16, 10.81) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Limb injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 13 | 1.0 | 1278 | 11 | 0.9 | 0.6760 | 0.84 ( 0.38, 1.88) | 0.84 ( 0.38, 1.89) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Pruritus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 23 | 1.8 | 1278 | 21 | 1.6 | 0.7530 | 0.91 ( 0.51, 1.64) | 0.91 ( 0.50, 1.65) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Skin ulcer

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 11 | 0.9 | 1278 | 17 | 1.3 | 0.2577 | 1.54 ( 0.72, | 3.28) | 1.55 ( 0.72, | 3.32) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Rash

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 13 | 1.0 | 1278 | 7 | 0.5 | 0.1757 | 0.54 ( 0.21, 1.34) | 0.53 ( 0.21, 1.34) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 57 | 4.5 | 1278 | 39 | 3.1 | 0.0590 | 0.68 ( 0.46, 1.02) | 0.67 ( 0.44, 1.02) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Insomnia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 27 | 2.1 | 1278 | 27 | 2.1 | 0.9907 | 1.00 ( 0.59, 1.69) | 1.00 ( 0.58, 1.71) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Depression

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 22 | 1.7 | 1278 | 17 | 1.3 | 0.4141 | 0.77 ( 0.41, 1.44) | 0.77 ( 0.41, 1.45) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Anxiety

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 13 | 1.0 | 1278 | 10 | 0.8 | 0.5248 | 0.77 ( 0.34, 1.74) | 0.76 ( 0.33, 1.75) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders
Preferred term: Cholelithiasis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 14 | 1.1 | 1278 | 10 | 0.8 | 0.4076 | 0.71 ( 0.32, 1.60) | 0.71 ( 0.31, 1.60) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders
Preferred term: Cataract

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 14 | 1.1 | 1278 | 11 | 0.9 | 0.5413 | 0.78 ( 0.36, 1.72) | 0.78 ( 0.35, 1.73) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Endocrine disorders
Preferred term: Hypothyroidism

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 29 | 2.3 | 1278 | 13 | 1.0 | 0.0124 | 0.45 ( 0.23, | 0.86) | 0.44 ( 0.23, | 0.85) | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | 0.4277 |
| Male | 958 | 21 | 2.2 | 975 | 8 | 0.8 | 0.0131 | 0.37 ( 0.17, | 0.84) | 0.37 ( 0.16, | 0.84) | -0.01 (-0.02, 0.00) | |
| Female | 316 | 8 | 2.5 | 303 | 5 | 1.7 | 0.4445 | 0.65 ( 0.22, | 1.97) | 0.65 ( 0.21, | 2.00) | -0.01 (-0.03, 0.01) | |
| Age [years] | | | | | | | | | | | | | 0.4650 |
| <65 | 435 | 11 | 2.5 | 392 | 3 | 0.8 | 0.0497 | 0.30 ( 0.09, | 1.08) | 0.30 ( 0.08, | 1.07) | -0.02 (-0.03, 0.00) | |
| >=65 | 839 | 18 | 2.1 | 886 | 10 | 1.1 | 0.0949 | 0.53 ( 0.24, | 1.13) | 0.52 ( 0.24, | 1.13) | -0.01 (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | 0.9195 |
| North America | 161 | 5 | 3.1 | 159 | 2 | 1.3 | 0.2586 | 0.41 ( 0.08, | 2.06) | 0.40 ( 0.08, | 2.08) | -0.02 (-0.05, 0.01) | |
| Latin America | 420 | 8 | 1.9 | 440 | 5 | 1.1 | 0.3559 | 0.60 ( 0.20, | 1.81) | 0.59 ( 0.19, | 1.82) | -0.01 (-0.02, 0.01) | |
| Europe | 469 | 8 | 1.7 | 467 | 4 | 0.9 | 0.2482 | 0.50 ( 0.15, | 1.66) | 0.50 ( 0.15, | 1.66) | -0.01 (-0.02, 0.01) | |
| Asia | 174 | 8 | 4.6 | 165 | 2 | 1.2 | 0.0656 | 0.26 ( 0.06, | 1.22) | 0.25 ( 0.05, | 1.22) | -0.03 (-0.07, 0.00) | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 ( 0.02, | 52.49) | 1.06 ( 0.02, | 54.66) | 0.00 (-0.04, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.0242 |
| Diabetic | 694 | 16 | 2.3 | 698 | 2 | 0.3 | 0.0009 | 0.12 ( 0.03, | 0.54) | 0.12 ( 0.03, | 0.53) | -0.02 (-0.03,-0.01) | |
| Non-Diabetic | 580 | 13 | 2.2 | 580 | 11 | 1.9 | 0.6799 | 0.85 ( 0.38, | 1.87) | 0.84 ( 0.37, | 1.90) | 0.00 (-0.02, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.0995 |
| <30 | 889 | 24 | 2.7 | 836 | 7 | 0.8 | 0.0036 | 0.31 ( 0.13, | 0.72) | 0.30 ( 0.13, | 0.71) | -0.02 (-0.03,-0.01) | |
| >=30 | 385 | 5 | 1.3 | 442 | 6 | 1.4 | 0.9413 | 1.05 ( 0.32, | 3.40) | 1.05 ( 0.32, | 3.45) | 0.00 (-0.02, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.5555 |
| <130 | 857 | 23 | 2.7 | 834 | 9 | 1.1 | 0.0155 | 0.40 ( 0.19, | 0.86) | 0.40 ( 0.18, | 0.86) | -0.02 (-0.03, 0.00) | |
| >=130 | 417 | 6 | 1.4 | 444 | 4 | 0.9 | 0.4616 | 0.63 ( 0.18, | 2.20) | 0.62 ( 0.17, | 2.22) | -0.01 (-0.02, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.8568 |
| <75 | 718 | 19 | 2.6 | 678 | 9 | 1.3 | 0.0790 | 0.50 ( 0.23, | 1.10) | 0.49 ( 0.22, | 1.10) | -0.01 (-0.03, 0.00) | |
| 75 to <85 | 348 | 6 | 1.7 | 382 | 2 | 0.5 | 0.1197 | 0.30 ( 0.06, | 1.49) | 0.30 ( 0.06, | 1.50) | -0.01 (-0.03, 0.00) | |
| >=85 | 208 | 4 | 1.9 | 218 | 2 | 0.9 | 0.3786 | 0.48 ( 0.09, | 2.58) | 0.47 ( 0.09, | 2.61) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Endocrine disorders
Preferred term: Hypothyroidism

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.0868 |
| <30 | 89 | 2 | 2.2 | 115 | 3 | 2.6 | 0.8685 | 1.16 ( 0.20, | 6.80) | 1.17 ( 0.19, | 7.13) | 0.00 (-0.04, 0.05) | |
| 30 to <45 | 348 | 14 | 4.0 | 345 | 1 | 0.3 | 0.0007 | 0.07 (<0.01, | 0.54) | 0.07 (<0.01, | 0.53) | -0.04 (-0.06,-0.02) | |
| >=45 | 837 | 13 | 1.6 | 818 | 9 | 1.1 | 0.4212 | 0.71 ( 0.30, | 1.65) | 0.71 ( 0.30, | 1.66) | 0.00 (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.5240 |
| Normal (<30) | 452 | 8 | 1.8 | 456 | 5 | 1.1 | 0.3931 | 0.62 ( 0.20, | 1.88) | 0.62 ( 0.20, | 1.90) | -0.01 (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 17 | 2.7 | 608 | 8 | 1.3 | 0.0817 | 0.49 ( 0.21, | 1.12) | 0.48 ( 0.20, | 1.12) | -0.01 (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 189 | 4 | 2.1 | 207 | 0 | 0 | 0.0569 | 0.10 (<0.01, | 1.87) | 0.10 (<0.01, | 1.86) | -0.02 (-0.04, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.2356 |
| Low, moderate or high | 953 | 17 | 1.8 | 947 | 10 | 1.1 | 0.1801 | 0.59 ( 0.27, | 1.29) | 0.59 ( 0.27, | 1.29) | -0.01 (-0.02, 0.00) | |
| Very high | 315 | 12 | 3.8 | 325 | 3 | 0.9 | 0.0158 | 0.24 ( 0.07, | 0.85) | 0.24 ( 0.07, | 0.84) | -0.03 (-0.05,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.5592 |
| No | 161 | 2 | 1.2 | 168 | 0 | 0 | 0.2313 | 0.19 (<0.01, | 3.96) | 0.19 (<0.01, | 3.97) | -0.01 (-0.03, 0.01) | |
| Yes | 1113 | 27 | 2.4 | 1110 | 13 | 1.2 | 0.0261 | 0.48 ( 0.25, | 0.93) | 0.48 ( 0.24, | 0.93) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.2704 |
| No | 62 | 0 | 0 | 72 | 1 | 1.4 | 0.5424 | 2.59 ( 0.11, | 62.43) | 2.62 ( 0.10, | 65.54) | 0.01 (-0.03, 0.05) | |
| Yes | 1212 | 29 | 2.4 | 1206 | 12 | 1.0 | 0.0078 | 0.42 ( 0.21, | 0.81) | 0.41 ( 0.21, | 0.81) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.1339 |
| No | 46 | 0 | 0 | 57 | 2 | 3.5 | 0.3207 | 4.05 ( 0.20, | 82.36) | 4.19 ( 0.20, | 89.46) | 0.03 (-0.03, 0.09) | |
| Yes | 1228 | 29 | 2.4 | 1221 | 11 | 0.9 | 0.0044 | 0.38 ( 0.19, | 0.76) | 0.38 ( 0.19, | 0.76) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Reproductive system and breast disorders
Preferred term: Benign prostatic hyperplasia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 15 | 1.2 | 1278 | 13 | 1.0 | 0.6977 | 0.86 ( 0.41, 1.81) | 0.86 ( 0.41, 1.82) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 375 | 29.4 | 1278 | 303 | 23.7 | 0.0011 | 0.81 ( 0.71, 0.92) | | 0.75 ( 0.62, 0.89) | | -0.06 (-0.09,-0.02) | |
| Sex | | | | | | | | | | | | | 0.6785 |
| Male | 958 | 285 | 29.7 | 975 | 237 | 24.3 | 0.0071 | 0.82 ( 0.71, 0.95) | | 0.76 ( 0.62, 0.93) | | -0.05 (-0.09,-0.01) | |
| Female | 316 | 90 | 28.5 | 303 | 66 | 21.8 | 0.0550 | 0.76 ( 0.58, 1.01) | | 0.70 ( 0.48, 1.01) | | -0.07 (-0.14, 0.00) | |
| Age [years] | | | | | | | | | | | | | 0.7813 |
| <65 | 435 | 138 | 31.7 | 392 | 98 | 25.0 | 0.0325 | 0.79 ( 0.63, 0.98) | | 0.72 ( 0.53, 0.97) | | -0.07 (-0.13,-0.01) | |
| >=65 | 839 | 237 | 28.2 | 886 | 205 | 23.1 | 0.0151 | 0.82 ( 0.70, 0.96) | | 0.76 ( 0.62, 0.95) | | -0.05 (-0.09,-0.01) | |
| Region | | | | | | | | | | | | | 0.3105 |
| North America | 161 | 31 | 19.3 | 159 | 28 | 17.6 | 0.7045 | 0.91 ( 0.58, 1.45) | | 0.90 ( 0.51, 1.58) | | -0.02 (-0.10, 0.07) | |
| Latin America | 420 | 128 | 30.5 | 440 | 106 | 24.1 | 0.0354 | 0.79 ( 0.63, 0.98) | | 0.72 ( 0.54, 0.98) | | -0.06 (-0.12, 0.00) | |
| Europe | 469 | 143 | 30.5 | 467 | 124 | 26.6 | 0.1822 | 0.87 ( 0.71, 1.07) | | 0.82 ( 0.62, 1.10) | | -0.04 (-0.10, 0.02) | |
| Asia | 174 | 66 | 37.9 | 165 | 37 | 22.4 | 0.0019 | 0.59 ( 0.42, 0.83) | | 0.47 ( 0.29, 0.76) | | -0.16 (-0.25,-0.06) | |
| Other | 50 | 7 | 14.0 | 47 | 8 | 17.0 | 0.6809 | 1.22 ( 0.48, 3.09) | | 1.26 ( 0.42, 3.80) | | 0.03 (-0.11, 0.17) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.4049 |
| Diabetic | 694 | 207 | 29.8 | 698 | 176 | 25.2 | 0.0540 | 0.85 ( 0.71, >1.00) | | 0.79 ( 0.63, 1.00) | | -0.05 (-0.09, 0.00) | |
| Non-Diabetic | 580 | 168 | 29.0 | 580 | 127 | 21.9 | 0.0057 | 0.76 ( 0.62, 0.92) | | 0.69 ( 0.53, 0.90) | | -0.07 (-0.12,-0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.3703 |
| <30 | 889 | 260 | 29.2 | 836 | 188 | 22.5 | 0.0014 | 0.77 ( 0.65, 0.90) | | 0.70 ( 0.56, 0.87) | | -0.07 (-0.11,-0.03) | |
| >=30 | 385 | 115 | 29.9 | 442 | 115 | 26.0 | 0.2175 | 0.87 ( 0.70, 1.08) | | 0.83 ( 0.61, 1.12) | | -0.04 (-0.10, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.7902 |
| <130 | 857 | 264 | 30.8 | 834 | 205 | 24.6 | 0.0043 | 0.80 ( 0.68, 0.93) | | 0.73 ( 0.59, 0.91) | | -0.06 (-0.10,-0.02) | |
| >=130 | 417 | 111 | 26.6 | 444 | 98 | 22.1 | 0.1199 | 0.83 ( 0.65, 1.05) | | 0.78 ( 0.57, 1.07) | | -0.05 (-0.10, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.5010 |
| <75 | 718 | 212 | 29.5 | 678 | 172 | 25.4 | 0.0821 | 0.86 ( 0.72, 1.02) | | 0.81 ( 0.64, 1.03) | | -0.04 (-0.09, 0.01) | |
| 75 to <85 | 348 | 100 | 28.7 | 382 | 85 | 22.3 | 0.0443 | 0.77 ( 0.60, 0.99) | | 0.71 ( 0.51, 0.99) | | -0.06 (-0.13, 0.00) | |
| >=85 | 208 | 63 | 30.3 | 218 | 46 | 21.1 | 0.0298 | 0.70 ( 0.50, 0.97) | | 0.62 ( 0.40, 0.96) | | -0.09 (-0.17,-0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3831 |
| <30 | 89 | 33 | 37.1 | 115 | 41 | 35.7 | 0.8335 | 0.96 ( 0.67, 1.39) | 0.94 ( 0.53, 1.67) | -0.01 (-0.15, 0.12) | |
| 30 to <45 | 348 | 101 | 29.0 | 345 | 86 | 24.9 | 0.2246 | 0.86 ( 0.67, 1.10) | 0.81 ( 0.58, 1.14) | -0.04 (-0.11, 0.03) | |
| >=45 | 837 | 241 | 28.8 | 818 | 176 | 21.5 | 0.0007 | 0.75 ( 0.63, 0.88) | 0.68 ( 0.54, 0.85) | -0.07 (-0.11,-0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.3393 |
| Normal (<30) | 452 | 110 | 24.3 | 456 | 91 | 20.0 | 0.1119 | 0.82 ( 0.64, 1.05) | 0.78 ( 0.57, 1.06) | -0.04 (-0.10, 0.01) | |
| Microalbuminuria (30 to <=300) | 627 | 186 | 29.7 | 608 | 156 | 25.7 | 0.1156 | 0.86 ( 0.72, 1.04) | 0.82 ( 0.64, 1.05) | -0.04 (-0.09, 0.01) | |
| Macroalbuminuria (>300) | 189 | 76 | 40.2 | 207 | 56 | 27.1 | 0.0055 | 0.67 ( 0.51, 0.89) | 0.55 ( 0.36, 0.84) | -0.13 (-0.22,-0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8373 |
| Low, moderate or high | 953 | 257 | 27.0 | 947 | 205 | 21.6 | 0.0069 | 0.80 ( 0.68, 0.94) | 0.75 ( 0.61, 0.92) | -0.05 (-0.09,-0.01) | |
| Very high | 315 | 115 | 36.5 | 325 | 98 | 30.2 | 0.0881 | 0.83 ( 0.66, 1.03) | 0.75 ( 0.54, 1.04) | -0.06 (-0.14, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.0690 |
| No | 161 | 41 | 25.5 | 168 | 47 | 28.0 | 0.6071 | 1.10 ( 0.77, 1.57) | 1.14 ( 0.70, 1.85) | 0.03 (-0.07, 0.12) | |
| Yes | 1113 | 334 | 30.0 | 1110 | 256 | 23.1 | 0.0002 | 0.77 ( 0.67, 0.88) | 0.70 ( 0.58, 0.85) | -0.07 (-0.11,-0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6613 |
| No | 62 | 17 | 27.4 | 72 | 18 | 25.0 | 0.7506 | 0.91 ( 0.52, 1.61) | 0.88 ( 0.41, 1.91) | -0.02 (-0.17, 0.13) | |
| Yes | 1212 | 358 | 29.5 | 1206 | 285 | 23.6 | 0.0010 | 0.80 ( 0.70, 0.91) | 0.74 ( 0.62, 0.88) | -0.06 (-0.09,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.0517 |
| No | 46 | 10 | 21.7 | 57 | 3 | 5.3 | 0.0123 | 0.24 ( 0.07, 0.83) | 0.20 ( 0.05, 0.78) | -0.16 (-0.30,-0.03) | |
| Yes | 1228 | 365 | 29.7 | 1221 | 300 | 24.6 | 0.0041 | 0.83 ( 0.73, 0.94) | 0.77 ( 0.64, 0.92) | -0.05 (-0.09,-0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 46 | 3.6 | 1278 | 26 | 2.0 | 0.0162 | 0.56 ( 0.35, 0.91) | 0.55 ( 0.34, 0.90) | -0.02 (-0.03, 0.00) | | |
| Sex | | | | | | | | | | | | 0.1559 |
| Male | 958 | 38 | 4.0 | 975 | 18 | 1.8 | 0.0055 | 0.47 ( 0.27, 0.81) | 0.46 ( 0.26, 0.80) | -0.02 (-0.04,-0.01) | | |
| Female | 316 | 8 | 2.5 | 303 | 8 | 2.6 | 0.9322 | 1.04 ( 0.40, 2.74) | 1.04 ( 0.39, 2.82) | 0.00 (-0.02, 0.03) | | |
| Age [years] | | | | | | | | | | | | 0.4978 |
| <65 | 435 | 14 | 3.2 | 392 | 9 | 2.3 | 0.4205 | 0.71 ( 0.31, 1.63) | 0.71 ( 0.30, 1.65) | -0.01 (-0.03, 0.01) | | |
| >=65 | 839 | 32 | 3.8 | 886 | 17 | 1.9 | 0.0179 | 0.50 ( 0.28, 0.90) | 0.49 ( 0.27, 0.90) | -0.02 (-0.03, 0.00) | | |
| Region | | | | | | | | | | | | 0.4613 |
| North America | 161 | 27 | 16.8 | 159 | 17 | 10.7 | 0.1144 | 0.64 ( 0.36, 1.12) | 0.59 ( 0.31, 1.14) | -0.06 (-0.14, 0.01) | | |
| Latin America | 420 | 9 | 2.1 | 440 | 3 | 0.7 | 0.0679 | 0.32 ( 0.09, 1.17) | 0.31 ( 0.08, 1.17) | -0.01 (-0.03, 0.00) | | |
| Europe | 469 | 5 | 1.1 | 467 | 6 | 1.3 | 0.7562 | 1.21 ( 0.37, 3.92) | 1.21 ( 0.37, 3.99) | 0.00 (-0.01, 0.02) | | |
| Asia | 174 | 4 | 2.3 | 165 | 0 | 0 | 0.0813 | 0.12 (<0.01, 2.16) | 0.11 (<0.01, 2.14) | -0.02 (-0.05, 0.00) | | |
| Other | 50 | 1 | 2.0 | 47 | 0 | 0 | 0.5020 | 0.35 ( 0.01, 8.48) | 0.35 ( 0.01, 8.74) | -0.02 (-0.07, 0.04) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.8888 |
| Diabetic | 694 | 29 | 4.2 | 698 | 16 | 2.3 | 0.0466 | 0.55 ( 0.30, >1.00) | 0.54 ( 0.29, 1.00) | -0.02 (-0.04, 0.00) | | |
| Non-Diabetic | 580 | 17 | 2.9 | 580 | 10 | 1.7 | 0.1728 | 0.59 ( 0.27, 1.27) | 0.58 ( 0.26, 1.28) | -0.01 (-0.03, 0.01) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.8569 |
| <30 | 889 | 28 | 3.1 | 836 | 14 | 1.7 | 0.0470 | 0.53 ( 0.28, >1.00) | 0.52 ( 0.27, 1.00) | -0.01 (-0.03, 0.00) | | |
| >=30 | 385 | 18 | 4.7 | 442 | 12 | 2.7 | 0.1326 | 0.58 ( 0.28, 1.19) | 0.57 ( 0.27, 1.20) | -0.02 (-0.05, 0.01) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1625 |
| <130 | 857 | 39 | 4.6 | 834 | 18 | 2.2 | 0.0064 | 0.47 ( 0.27, 0.82) | 0.46 ( 0.26, 0.82) | -0.02 (-0.04,-0.01) | | |
| >=130 | 417 | 7 | 1.7 | 444 | 8 | 1.8 | 0.8902 | 1.07 ( 0.39, 2.93) | 1.07 ( 0.39, 2.99) | 0.00 (-0.02, 0.02) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2619 |
| <75 | 718 | 23 | 3.2 | 678 | 17 | 2.5 | 0.4360 | 0.78 ( 0.42, 1.45) | 0.78 ( 0.41, 1.47) | -0.01 (-0.02, 0.01) | | |
| 75 to <85 | 348 | 13 | 3.7 | 382 | 4 | 1.0 | 0.0161 | 0.28 ( 0.09, 0.85) | 0.27 ( 0.09, 0.84) | -0.03 (-0.05, 0.00) | | |
| >=85 | 208 | 10 | 4.8 | 218 | 5 | 2.3 | 0.1593 | 0.48 ( 0.17, 1.37) | 0.46 ( 0.16, 1.38) | -0.03 (-0.06, 0.01) | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.5211 |
| <30 | 89 | 3 | 3.4 | 115 | 1 | 0.9 | 0.2013 | 0.26 ( 0.03, 2.44) | 0.25 ( 0.03, 2.46) | -0.03 (-0.07, 0.02) | |
| 30 to <45 | 348 | 11 | 3.2 | 345 | 9 | 2.6 | 0.6642 | 0.83 ( 0.35, 1.97) | 0.82 ( 0.34, 2.01) | -0.01 (-0.03, 0.02) | |
| >=45 | 837 | 32 | 3.8 | 818 | 16 | 2.0 | 0.0236 | 0.51 ( 0.28, 0.93) | 0.50 ( 0.27, 0.92) | -0.02 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.4290 |
| Normal (<30) | 452 | 7 | 1.5 | 456 | 7 | 1.5 | 0.9867 | 0.99 ( 0.35, 2.80) | 0.99 ( 0.34, 2.85) | 0.00 (-0.02, 0.02) | |
| Microalbuminuria (30 to <=300) | 627 | 32 | 5.1 | 608 | 14 | 2.3 | 0.0094 | 0.45 ( 0.24, 0.84) | 0.44 ( 0.23, 0.83) | -0.03 (-0.05,-0.01) | |
| Macroalbuminuria (>300) | 189 | 7 | 3.7 | 207 | 5 | 2.4 | 0.4551 | 0.65 ( 0.21, 2.02) | 0.64 ( 0.20, 2.06) | -0.01 (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.5673 |
| Low, moderate or high | 953 | 35 | 3.7 | 947 | 18 | 1.9 | 0.0190 | 0.52 ( 0.30, 0.91) | 0.51 ( 0.29, 0.90) | -0.02 (-0.03, 0.00) | |
| Very high | 315 | 11 | 3.5 | 325 | 8 | 2.5 | 0.4425 | 0.70 ( 0.29, 1.73) | 0.70 ( 0.28, 1.76) | -0.01 (-0.04, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.4634 |
| No | 161 | 10 | 6.2 | 168 | 4 | 2.4 | 0.0853 | 0.38 ( 0.12, 1.20) | 0.37 ( 0.11, 1.20) | -0.04 (-0.08, 0.01) | |
| Yes | 1113 | 36 | 3.2 | 1110 | 22 | 2.0 | 0.0640 | 0.61 ( 0.36, 1.03) | 0.60 ( 0.35, 1.04) | -0.01 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.3755 |
| No | 62 | 6 | 9.7 | 72 | 2 | 2.8 | 0.0928 | 0.29 ( 0.06, 1.37) | 0.27 ( 0.05, 1.37) | -0.07 (-0.15, 0.01) | |
| Yes | 1212 | 40 | 3.3 | 1206 | 24 | 2.0 | 0.0448 | 0.60 ( 0.37, 0.99) | 0.59 ( 0.36, 0.99) | -0.01 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.7959 |
| No | 46 | 1 | 2.2 | 57 | 1 | 1.8 | 0.8781 | 0.81 ( 0.05, 12.55) | 0.80 ( 0.05, 13.21) | 0.00 (-0.06, 0.05) | |
| Yes | 1228 | 45 | 3.7 | 1221 | 25 | 2.0 | 0.0163 | 0.56 ( 0.34, 0.91) | 0.55 ( 0.33, 0.90) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 40 | 3.1 | 1278 | 43 | 3.4 | 0.7488 | 1.07 ( 0.70, 1.64) | 1.07 ( 0.69, 1.66) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1274 | 38 | 3.0 | 1278 | 18 | 1.4 | 0.0066 | 0.47 ( 0.27, 0.82) | 0.46 ( 0.26, 0.82) | -0.02 (-0.03, 0.00) | | |
| Sex | | | | | | | | | | | | 0.6043 |
| Male | 958 | 29 | 3.0 | 975 | 15 | 1.5 | 0.0282 | 0.51 ( 0.27, 0.94) | 0.50 ( 0.27, 0.94) | -0.01 (-0.03, 0.00) | | |
| Female | 316 | 9 | 2.8 | 303 | 3 | 1.0 | 0.0937 | 0.35 ( 0.10, 1.27) | 0.34 ( 0.09, 1.27) | -0.02 (-0.04, 0.00) | | |
| Age [years] | | | | | | | | | | | | 0.4210 |
| <65 | 435 | 10 | 2.3 | 392 | 6 | 1.5 | 0.4232 | 0.67 ( 0.24, 1.82) | 0.66 ( 0.24, 1.83) | -0.01 (-0.03, 0.01) | | |
| >=65 | 839 | 28 | 3.3 | 886 | 12 | 1.4 | 0.0062 | 0.41 ( 0.21, 0.79) | 0.40 ( 0.20, 0.79) | -0.02 (-0.03,-0.01) | | |
| Region | | | | | | | | | | | | 0.8562 |
| North America | 161 | 12 | 7.5 | 159 | 8 | 5.0 | 0.3708 | 0.68 ( 0.28, 1.61) | 0.66 ( 0.26, 1.66) | -0.02 (-0.08, 0.03) | | |
| Latin America | 420 | 6 | 1.4 | 440 | 2 | 0.5 | 0.1369 | 0.32 ( 0.06, 1.57) | 0.32 ( 0.06, 1.57) | -0.01 (-0.02, 0.00) | | |
| Europe | 469 | 14 | 3.0 | 467 | 5 | 1.1 | 0.0378 | 0.36 ( 0.13, 0.99) | 0.35 ( 0.13, 0.98) | -0.02 (-0.04, 0.00) | | |
| Asia | 174 | 6 | 3.4 | 165 | 3 | 1.8 | 0.3507 | 0.53 ( 0.13, 2.07) | 0.52 ( 0.13, 2.11) | -0.02 (-0.05, 0.02) | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | 0.9757 | 1.06 ( 0.02, 52.49) | 1.06 ( 0.02, 54.66) | 0.00 (-0.04, 0.04) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9919 |
| Diabetic | 694 | 19 | 2.7 | 698 | 9 | 1.3 | 0.0543 | 0.47 ( 0.21, 1.03) | 0.46 ( 0.21, 1.03) | -0.01 (-0.03, 0.00) | | |
| Non-Diabetic | 580 | 19 | 3.3 | 580 | 9 | 1.6 | 0.0557 | 0.47 ( 0.22, 1.04) | 0.47 ( 0.21, 1.04) | -0.02 (-0.03, 0.00) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.8857 |
| <30 | 889 | 18 | 2.0 | 836 | 8 | 1.0 | 0.0689 | 0.47 ( 0.21, 1.08) | 0.47 ( 0.20, 1.08) | -0.01 (-0.02, 0.00) | | |
| >=30 | 385 | 20 | 5.2 | 442 | 10 | 2.3 | 0.0245 | 0.44 ( 0.21, 0.92) | 0.42 ( 0.20, 0.91) | -0.03 (-0.06, 0.00) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8151 |
| <130 | 857 | 27 | 3.2 | 834 | 13 | 1.6 | 0.0313 | 0.49 ( 0.26, 0.95) | 0.49 ( 0.25, 0.95) | -0.02 (-0.03, 0.00) | | |
| >=130 | 417 | 11 | 2.6 | 444 | 5 | 1.1 | 0.1007 | 0.43 ( 0.15, 1.22) | 0.42 ( 0.14, 1.22) | -0.02 (-0.03, 0.00) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.1442 |
| <75 | 718 | 18 | 2.5 | 678 | 13 | 1.9 | 0.4550 | 0.76 ( 0.38, 1.55) | 0.76 ( 0.37, 1.56) | -0.01 (-0.02, 0.01) | | |
| 75 to <85 | 348 | 14 | 4.0 | 382 | 4 | 1.0 | 0.0096 | 0.26 ( 0.09, 0.78) | 0.25 ( 0.08, 0.77) | -0.03 (-0.05,-0.01) | | |
| >=85 | 208 | 6 | 2.9 | 218 | 1 | 0.5 | 0.0490 | 0.16 ( 0.02, 1.31) | 0.16 ( 0.02, 1.30) | -0.02 (-0.05, 0.00) | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.2363 |
| <30 | 89 | 0 | 0 | 115 | 3 | 2.6 | 0.2041 | 5.43 ( 0.28,103.80) | 5.57 ( 0.28,109.22) | 0.02 (-0.01, 0.06) | |
| 30 to <45 | 348 | 12 | 3.4 | 345 | 5 | 1.4 | 0.0890 | 0.42 ( 0.15, 1.18) | 0.41 ( 0.14, 1.18) | -0.02 (-0.04, 0.00) | |
| >=45 | 837 | 26 | 3.1 | 818 | 10 | 1.2 | 0.0086 | 0.39 ( 0.19, 0.81) | 0.39 ( 0.18, 0.81) | -0.02 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.9610 |
| Normal (<30) | 452 | 12 | 2.7 | 456 | 6 | 1.3 | 0.1478 | 0.50 ( 0.19, 1.31) | 0.49 ( 0.18, 1.31) | -0.01 (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 627 | 21 | 3.3 | 608 | 9 | 1.5 | 0.0329 | 0.44 ( 0.20, 0.96) | 0.43 ( 0.20, 0.95) | -0.02 (-0.04, 0.00) | |
| Macroalbuminuria (>300) | 189 | 5 | 2.6 | 207 | 3 | 1.4 | 0.3980 | 0.55 ( 0.13, 2.26) | 0.54 ( 0.13, 2.30) | -0.01 (-0.04, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.3500 |
| Low, moderate or high | 953 | 30 | 3.1 | 947 | 12 | 1.3 | 0.0053 | 0.40 ( 0.21, 0.78) | 0.39 ( 0.20, 0.78) | -0.02 (-0.03,-0.01) | |
| Very high | 315 | 8 | 2.5 | 325 | 6 | 1.8 | 0.5487 | 0.73 ( 0.26, 2.07) | 0.72 ( 0.25, 2.10) | -0.01 (-0.03, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.5969 |
| No | 161 | 6 | 3.7 | 168 | 4 | 2.4 | 0.4772 | 0.64 ( 0.18, 2.22) | 0.63 ( 0.17, 2.28) | -0.01 (-0.05, 0.02) | |
| Yes | 1113 | 32 | 2.9 | 1110 | 14 | 1.3 | 0.0075 | 0.44 ( 0.24, 0.82) | 0.43 ( 0.23, 0.81) | -0.02 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.4950 |
| No | 62 | 2 | 3.2 | 72 | 0 | 0 | 0.1936 | 0.17 (<0.01, 3.53) | 0.17 (<0.01, 3.54) | -0.03 (-0.08, 0.02) | |
| Yes | 1212 | 36 | 3.0 | 1206 | 18 | 1.5 | 0.0139 | 0.50 ( 0.29, 0.88) | 0.49 ( 0.28, 0.88) | -0.01 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.7181 |
| No | 46 | 1 | 2.2 | 57 | 0 | 0 | 0.3852 | 0.27 ( 0.01, 6.48) | 0.26 ( 0.01, 6.63) | -0.02 (-0.08, 0.03) | |
| Yes | 1228 | 37 | 3.0 | 1221 | 18 | 1.5 | 0.0102 | 0.49 ( 0.28, 0.85) | 0.48 ( 0.27, 0.85) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 27 | 2.1 | 1278 | 20 | 1.6 | 0.2977 | 0.74 ( 0.42, 1.31) | 0.73 ( 0.41, 1.32) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure chronic

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 25 | 2.0 | 1278 | 19 | 1.5 | 0.3560 | 0.76 ( 0.42, 1.37) | 0.75 ( 0.41, 1.38) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 16 | 1.3 | 1278 | 15 | 1.2 | 0.8497 | 0.93 ( 0.46, 1.88) | 0.93 ( 0.46, 1.90) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 10 | 0.8 | 1278 | 14 | 1.1 | 0.4164 | 1.40 ( 0.62, 3.13) | 1.40 ( 0.62, 3.16) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 58 | 4.6 | 1278 | 55 | 4.3 | 0.7598 | 0.95 ( 0.66, 1.36) | 0.94 ( 0.65, 1.38) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 14 | 1.1 | 1278 | 14 | 1.1 | 0.9933 | 1.00 ( 0.48, 2.08) | 1.00 ( 0.47, 2.10) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Septic shock

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 6 | 0.5 | 1278 | 13 | 1.0 | 0.1085 | 2.16 ( 0.82, 5.66) | 2.17 ( 0.82, 5.73) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 54 | 4.2 | 1278 | 39 | 3.1 | 0.1096 | 0.72 ( 0.48, 1.08) | 0.71 ( 0.47, 1.08) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal impairment

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 27 | 2.1 | 1278 | 20 | 1.6 | 0.2977 | 0.74 ( 0.42, 1.31) | 0.73 ( 0.41, 1.32) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 16 | 1.3 | 1278 | 7 | 0.5 | 0.0584 | 0.44 ( 0.18, 1.06) | 0.43 ( 0.18, 1.06) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 9 | 0.7 | 1278 | 16 | 1.3 | 0.1618 | 1.77 ( 0.79, 4.00) | 1.78 ( 0.78, 4.05) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Syncope

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 7 | 0.5 | 1278 | 14 | 1.1 | 0.1269 | 1.99 ( 0.81, 4.92) | 2.00 ( 0.81, 4.98) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 30 | 2.4 | 1278 | 25 | 2.0 | 0.4881 | 0.83 ( 0.49, 1.40) | 0.83 ( 0.48, 1.41) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 14 | 1.1 | 1278 | 14 | 1.1 | 0.9933 | 1.00 ( 0.48, 2.08) | 1.00 ( 0.47, 2.10) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 8 | 0.6 | 1278 | 16 | 1.3 | 0.1025 | 1.99 ( 0.86, 4.64) | 2.01 ( 0.86, 4.70) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 158 | 12.4 | 1278 | 139 | 10.9 | 0.2295 | 0.88 | ( 0.71, 1.09) | 0.86 | ( 0.68, 1.10) | -0.02 | (-0.04,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 23 | 1.8 | 1278 | 14 | 1.1 | 0.1336 | 0.61 | ( 0.31, 1.17) | 0.60 | ( 0.31, 1.18) | -0.01 | (-0.02,0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 15 | 1.2 | 1278 | 18 | 1.4 | 0.6054 | 1.20 | ( 0.61, 2.36) | 1.20 | ( 0.60, 2.39) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 17 | 1.3 | 1278 | 15 | 1.2 | 0.7153 | 0.88 | ( 0.44, 1.75) | 0.88 | ( 0.44, 1.77) | 0.00 | (-0.01,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 13 | 1.0 | 1278 | 4 | 0.3 | 0.0280 | 0.31 | ( 0.10, | 0.94) | 0.30 | ( 0.10, 0.94) | -0.01 | (-0.01,0.00) | |
| Sex | | | | | | | | | | | | | | | 0.4083 |
| Male | 958 | 9 | 0.9 | 975 | 4 | 0.4 | 0.1546 | 0.44 | ( 0.13, | 1.41) | 0.43 | ( 0.13, 1.42) | -0.01 | (-0.01,0.00) | |
| Female | 316 | 4 | 1.3 | 303 | 0 | 0 | 0.0802 | 0.12 | (<0.01, | 2.14) | 0.11 | (<0.01, 2.13) | -0.01 | (-0.03,0.00) | |
| Age [years] | | | | | | | | | | | | | | | |
| <65 | 435 | 6 | 1.4 | 392 | 3 | 0.8 | | | | | | | | | |
| >=65 | 839 | 7 | 0.8 | 886 | 1 | 0.1 | | | | | | | | | |
| Region | | | | | | | | | | | | | | | |
| North America | 161 | 6 | 3.7 | 159 | 2 | 1.3 | | | | | | | | | |
| Latin America | 420 | 3 | 0.7 | 440 | 1 | 0.2 | | | | | | | | | |
| Europe | 469 | 2 | 0.4 | 467 | 1 | 0.2 | | | | | | | | | |
| Asia | 174 | 2 | 1.1 | 165 | 0 | 0 | | | | | | | | | |
| Other | 50 | 0 | 0 | 47 | 0 | 0 | | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | |
| Diabetic | 694 | 7 | 1.0 | 698 | 1 | 0.1 | | | | | | | | | |
| Non-Diabetic | 580 | 6 | 1.0 | 580 | 3 | 0.5 | | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | |
| <30 | 889 | 7 | 0.8 | 836 | 1 | 0.1 | | | | | | | | | |
| >=30 | 385 | 6 | 1.6 | 442 | 3 | 0.7 | | | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | 0.9907 |
| <130 | 857 | 10 | 1.2 | 834 | 3 | 0.4 | 0.0574 | 0.31 | ( 0.09, | 1.12) | 0.31 | ( 0.08, 1.11) | -0.01 | (-0.02,0.00) | |
| >=130 | 417 | 3 | 0.7 | 444 | 1 | 0.2 | 0.2866 | 0.31 | ( 0.03, | 3.00) | 0.31 | ( 0.03, 3.01) | 0.00 | (-0.01,0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | |
| <75 | 718 | 5 | 0.7 | 678 | 1 | 0.1 | | | | | | | | | |
| 75 to <85 | 348 | 4 | 1.1 | 382 | 3 | 0.8 | | | | | | | | | |
| >=85 | 208 | 4 | 1.9 | 218 | 0 | 0 | | | | | | | | | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8858 |
| <30 | 89 | 0 | 0 | 115 | 0 | 0 | 0.8985 | 0.78 | ( 0.02, 38.72) | 0.77 | ( 0.02, 39.43) | 0.00 | (-0.02,0.02) | |
| 30 to <45 | 348 | 4 | 1.1 | 345 | 1 | 0.3 | 0.1813 | 0.25 | ( 0.03, 2.24) | 0.25 | ( 0.03, 2.25) | -0.01 | (-0.02,0.00) | |
| >=45 | 837 | 9 | 1.1 | 818 | 3 | 0.4 | 0.0894 | 0.34 | ( 0.09, 1.26) | 0.34 | ( 0.09, 1.26) | -0.01 | (-0.02,0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | |
| Normal (<30) | 452 | 6 | 1.3 | 456 | 0 | 0 | | | | | | | | |
| Microalbuminuria (30 to <=300) | 627 | 4 | 0.6 | 608 | 4 | 0.7 | | | | | | | | |
| Macroalbuminuria (>300) | 189 | 3 | 1.6 | 207 | 0 | 0 | | | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.6812 |
| Low, moderate or high | 953 | 11 | 1.2 | 947 | 3 | 0.3 | 0.0328 | 0.27 | ( 0.08, 0.98) | 0.27 | ( 0.08, 0.98) | -0.01 | (-0.02,0.00) | |
| Very high | 315 | 2 | 0.6 | 325 | 1 | 0.3 | 0.5446 | 0.48 | ( 0.04, 5.32) | 0.48 | ( 0.04, 5.35) | 0.00 | (-0.01,0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3870 |
| No | 161 | 1 | 0.6 | 168 | 1 | 0.6 | 0.9759 | 0.96 | ( 0.06, 15.19) | 0.96 | ( 0.06, 15.45) | 0.00 | (-0.02,0.02) | |
| Yes | 1113 | 12 | 1.1 | 1110 | 3 | 0.3 | 0.0200 | 0.25 | ( 0.07, 0.89) | 0.25 | ( 0.07, 0.88) | -0.01 | (-0.01,0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9296 |
| No | 62 | 1 | 1.6 | 72 | 0 | 0 | 0.4126 | 0.29 | ( 0.01, 6.94) | 0.28 | ( 0.01, 7.07) | -0.02 | (-0.06,0.03) | |
| Yes | 1212 | 12 | 1.0 | 1206 | 4 | 0.3 | 0.0459 | 0.33 | ( 0.11, 1.04) | 0.33 | ( 0.11, 1.03) | -0.01 | (-0.01,0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6420 |
| No | 46 | 0 | 0 | 57 | 0 | 0 | 0.9157 | 0.81 | ( 0.02, 40.07) | 0.81 | ( 0.02, 41.54) | 0.00 | (-0.04,0.04) | |
| Yes | 1228 | 13 | 1.1 | 1221 | 4 | 0.3 | 0.0294 | 0.31 | ( 0.10, 0.95) | 0.31 | ( 0.10, 0.94) | -0.01 | (-0.01,0.00) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 36 | 2.8 | 1278 | 28 | 2.2 | 0.3051 | 0.78 | ( 0.48, 1.26) | 0.77 | ( 0.47, 1.27) | -0.01 (-0.02,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 30 | 2.4 | 1278 | 25 | 2.0 | 0.4881 | 0.83 | ( 0.49, 1.40) | 0.83 | ( 0.48, 1.41) | 0.00 | (-0.02,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1274 | 26 | 2.0 | 1278 | 20 | 1.6 | 0.3663 | 0.77 | ( 0.43, 1.37) | 0.76 | ( 0.42, 1.37) | 0.00 | (-0.02,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.3.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal impairment

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1274 | 14 | 1.1 | 1278 | 12 | 0.9 | 0.6875 | 0.85 | ( 0.40, 1.84) | 0.85 | ( 0.39, 1.85) | 0.00 (-0.01,0.01) | |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

R.3.2.6 Medical concepts for adverse events of special interest and other specific AEs

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Broad BIcMQ 'Urinary tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)' | Urinary tract malignancy events (BIcMQ) | 40000010 | | 10004986 | Bladder adenocarcinoma recurrent |
| | | | | 10004987 | Bladder adenocarcinoma stage 0 |
| | | | | 10004988 | Bladder adenocarcinoma stage I |
| | | | | 10004989 | Bladder adenocarcinoma stage II |
| | | | | 10004990 | Bladder adenocarcinoma stage III |
| | | | | 10004991 | Bladder adenocarcinoma stage IV |
| | | | | 10004992 | Bladder adenocarcinoma stage unspecified |
| | | | | 10005003 | Bladder cancer |
| | | | | 10005005 | Bladder cancer recurrent |
| | | | | 10005006 | Bladder cancer stage 0, with cancer in situ |
| | | | | 10005007 | Bladder cancer stage 0, without cancer in situ |
| | | | | 10005008 | Bladder cancer stage I, with cancer in situ |
| | | | | 10005009 | Bladder cancer stage I, without cancer in situ |
| | | | | 10005010 | Bladder cancer stage II |
| | | | | 10005011 | Bladder cancer stage III |
| | | | | 10005012 | Bladder cancer stage IV |
| | | | | 10005056 | Bladder neoplasm |
| | | | | 10005075 | Bladder squamous cell carcinoma recurrent |
| | | | | 10005076 | Bladder squamous cell carcinoma stage 0 |
| | | | | 10005077 | Bladder squamous cell carcinoma stage I |
| | | | | 10005078 | Bladder squamous cell carcinoma stage II |
| | | | | 10005079 | Bladder squamous cell carcinoma stage III |
| | | | | 10005080 | Bladder squamous cell carcinoma stage IV |
| | | | | 10005081 | Bladder squamous cell carcinoma stage unspecified |
| | | | | 10005084 | Bladder transitional cell carcinoma |
| | | | | 10009253 | Clear cell sarcoma of the kidney |
| | | | | 10026426 | Malignant neoplasm of renal pelvis |
| | | | | 10027455 | Metastases to kidney |
| | | | | 10029145 | Nephroblastoma |
| | | | | 10033702 | Papillary tumour of renal pelvis |
| | | | | 10038389 | Renal cancer |
| | | | | 10038390 | Renal cancer recurrent |
| | | | | 10038391 | Renal cancer stage I |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Broad BIcMQ 'Urinary tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)' | Urinary tract malignancy events (BIcMQ) | 40000010 | | 10038392 | Renal cancer stage II |
| | | | | 10038393 | Renal cancer stage III |
| | | | | 10038394 | Renal cancer stage IV |
| | | | | 10038410 | Renal cell carcinoma recurrent |
| | | | | 10038411 | Renal cell carcinoma stage I |
| | | | | 10038412 | Renal cell carcinoma stage II |
| | | | | 10038413 | Renal cell carcinoma stage III |
| | | | | 10038414 | Renal cell carcinoma stage IV |
| | | | | 10039019 | Rhabdoid tumour of the kidney |
| | | | | 10044406 | Transitional cell cancer of renal pelvis and ureter metastatic |
| | | | | 10044407 | Transitional cell cancer of the renal pelvis and ureter |
| | | | | 10044408 | Transitional cell cancer of the renal pelvis and ureter localised |
| | | | | 10044410 | Transitional cell cancer of the renal pelvis and ureter recurrent |
| | | | | 10044411 | Transitional cell cancer of the renal pelvis and ureter regional |
| | | | | 10044412 | Transitional cell carcinoma |
| | | | | 10044426 | Transitional cell carcinoma urethra |
| | | | | 10046392 | Ureteric cancer |
| | | | | 10046393 | Ureteric cancer local |
| | | | | 10046394 | Ureteric cancer metastatic |
| | | | | 10046396 | Ureteric cancer recurrent |
| | | | | 10046397 | Ureteric cancer regional |
| | | | | 10046431 | Urethral cancer |
| | | | | 10046433 | Urethral cancer metastatic |
| | | | | 10046435 | Urethral cancer recurrent |
| | | | | 10049722 | Metastases to bladder |
| | | | | 10050018 | Renal cancer metastatic |
| | | | | 10050513 | Metastatic renal cell carcinoma |
| | | | | 10051690 | Urinary bladder sarcoma |
| | | | | 10051948 | Renal adenoma |
| | | | | 10056251 | Metastases to urinary tract |
| | | | | 10057352 | Metastatic carcinoma of the bladder |
| | | | | 10061183 | Genitourinary tract neoplasm |
| | | | | 10061272 | Malignant urinary tract neoplasm |
| | | | | 10061396 | Urinary tract carcinoma in situ |
| | | | | 10061398 | Urinary tract neoplasm |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Broad BIcMQ 'Urinary tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)' | Urinary tract malignancy events (BIcMQ) | 40000010 | | 10061482 | Renal neoplasm |
| | | | | 10061872 | Non-renal cell carcinoma of kidney |
| | | | | 10062221 | Ureteral neoplasm |
| | | | | 10062223 | Urethral neoplasm |
| | | | | 10066749 | Bladder transitional cell carcinoma stage 0 |
| | | | | 10066750 | Bladder transitional cell carcinoma recurrent |
| | | | | 10066751 | Bladder transitional cell carcinoma stage I |
| | | | | 10066752 | Bladder transitional cell carcinoma stage IV |
| | | | | 10066753 | Bladder transitional cell carcinoma stage II |
| | | | | 10066754 | Bladder transitional cell carcinoma stage III |
| | | | | 10067943 | Hereditary papillary renal carcinoma |
| | | | | 10067944 | Hereditary leiomyomatosis renal cell carcinoma |
| | | | | 10067946 | Renal cell carcinoma |
| | | | | 10069359 | Leukaemic infiltration renal |
| | | | | 10070179 | Denys-Drash syndrome |
| | | | | 10071080 | Transitional cell carcinoma metastatic |
| | | | | 10071664 | Bladder transitional cell carcinoma metastatic |
| | | | | 10072793 | Urethral melanoma metastatic |
| | | | | 10073251 | Clear cell renal cell carcinoma |
| | | | | 10074419 | Malignant genitourinary tract neoplasm |
| | | | | 10077051 | Transitional cell carcinoma recurrent |
| | | | | 10077166 | Genitourinary melanoma |
| | | | | 10078341 | Neuroendocrine carcinoma of the bladder |
| | | | | 10078493 | Papillary renal cell carcinoma |
| | | | | 10080544 | Chromophobe renal cell carcinoma |
| | | | | 10081895 | Multilocular cystic nephroma |
| | | | | 10085663 | Clear cell papillary renal cell carcinoma |
| | | | | 10086817 | Malignant urinary tract neoplasm metastatic |

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MedDRA version: 25.0

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures (BIcMQ)' | Bone fracture events (BIcMQ) | 40000012 | | 10000397 | Acetabulum fracture |
| | | | | 10002544 | Ankle fracture |
| | | | | 10009245 | Clavicle fracture |
| | | | | 10009506 | Closed fracture manipulation |
| | | | | 10010149 | Complicated fracture |
| | | | | 10010214 | Compression fracture |
| | | | | 10015741 | External fixation of fracture |
| | | | | 10016042 | Facial bones fracture |
| | | | | 10016450 | Femoral neck fracture |
| | | | | 10016454 | Femur fracture |
| | | | | 10016667 | Fibula fracture |
| | | | | 10016747 | Flail chest |
| | | | | 10016970 | Foot fracture |
| | | | | 10016997 | Forearm fracture |
| | | | | 10017076 | Fracture |
| | | | | 10017081 | Fracture delayed union |
| | | | | 10017085 | Fracture malunion |
| | | | | 10017088 | Fracture nonunion |
| | | | | 10017107 | Fracture of clavicle due to birth trauma |
| | | | | 10017296 | Fractured maxilla elevation |
| | | | | 10017308 | Fractured sacrum |
| | | | | 10017310 | Fractured skull depressed |
| | | | | 10018720 | Greenstick fracture |
| | | | | 10019114 | Hand fracture |
| | | | | 10020100 | Hip fracture |
| | | | | 10020462 | Humerus fracture |
| | | | | 10021343 | Ilium fracture |
| | | | | 10022576 | Internal fixation of fracture |
| | | | | 10023149 | Jaw fracture |
| | | | | 10028200 | Multiple fractures |
| | | | | 10030527 | Open fracture |
| | | | | 10030682 | Open reduction of fracture |
| | | | | 10030684 | Open reduction of spinal fracture |
| | | | | 10031290 | Osteoporotic fracture |
| | | | | 10034122 | Patella fracture |
| | | | | 10034156 | Pathological fracture |
| | | | | 10037802 | Radius fracture |
| | | | | 10039117 | Rib fracture |
| | | | | 10039579 | Scapula fracture |
| | | | | 10040960 | Skull fractured base |
| | | | | 10041541 | Spinal compression fracture |

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| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures (BIcMQ)' | Bone fracture events (BIcMQ) | 40000012 | | 10041569 | Spinal fracture |
| | | | | 10042015 | Sternal fracture |
| | | | | 10042212 | Stress fracture |
| | | | | 10043827 | Tibia fracture |
| | | | | 10045375 | Ulna fracture |
| | | | | 10048049 | Wrist fracture |
| | | | | 10048617 | Pseudarthrosis |
| | | | | 10049164 | Fractured coccyx |
| | | | | 10049514 | Traumatic fracture |
| | | | | 10049946 | Cervical vertebral fracture |
| | | | | 10049947 | Lumbar vertebral fracture |
| | | | | 10049948 | Thoracic vertebral fracture |
| | | | | 10052614 | Comminuted fracture |
| | | | | 10053206 | Fracture displacement |
| | | | | 10053962 | Epiphyseal fracture |
| | | | | 10057147 | Fracture debridement |
| | | | | 10057609 | Fracture reduction |
| | | | | 10059362 | Fractured zygomatic arch elevation |
| | | | | 10061161 | Pelvic fracture |
| | | | | 10061365 | Skull fracture |
| | | | | 10061394 | Upper limb fracture |
| | | | | 10061599 | Lower limb fracture |
| | | | | 10061959 | Fracture treatment |
| | | | | 10064210 | Bone fissure |
| | | | | 10064211 | Bone fragmentation |
| | | | | 10066094 | Torus fracture |
| | | | | 10066184 | Avulsion fracture |
| | | | | 10066386 | Impacted fracture |
| | | | | 10069066 | Intramedullary rod insertion |
| | | | | 10069135 | Periprosthetic fracture |
| | | | | 10069723 | Loss of anatomical alignment after fracture reduction |
| | | | | 10070884 | Atypical femur fracture |
| | | | | 10072132 | Fracture pain |
| | | | | 10072395 | Atypical fracture |
| | | | | 10073162 | Chance fracture |
| | | | | 10073853 | Osteochondral fracture |
| | | | | 10074362 | Sacroiliac fracture |
| | | | | 10074551 | Limb fracture |
| | | | | 10074807 | Spinal fusion fracture |
| | | | | 10077270 | Surgical fixation of rib fracture |

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Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures (BIcMQ)' | Bone fracture events (BIcMQ) | 40000012 | | 10077603 | Craniofacial fracture |
| | | | | 10078749 | Lisfranc fracture |
| | | | | 10079423 | Fracture blisters |
| | | | | 10079667 | Metaphyseal corner fracture |
| | | | | 10079813 | Fracture infection |
| | | | | 10079864 | Subchondral insufficiency fracture |
| | | | | 10080550 | Osteophyte fracture |
| | | | | 10081343 | Maisonneuve fracture |
| | | | | 10081442 | Stapes fracture |
| | | | | 10083585 | Skull fracture treatment |
| | | | | 10083586 | Spinal fracture treatment |
| | | | | 10085543 | Neurogenic fracture |
| | | | | 10085774 | Microfracture surgery |
| | | | | 10087273 | Depressed fracture |
| Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)' | Genital infections (BIcMQ) | 40000004 | | 10004055 | Bacterial vaginosis |
| | | | | 10004074 | Balanitis candida |
| | | | | 10004078 | Balanoposthitis |
| | | | | 10004138 | Bartholin's abscess |
| | | | | 10004142 | Bartholinitis |
| | | | | 10008323 | Cervicitis |
| | | | | 10014791 | Endometritis |
| | | | | 10015000 | Epididymitis |
| | | | | 10015001 | Epididymitis blastomyces |
| | | | | 10018143 | Genital candidiasis |
| | | | | 10020497 | Hydrocele male infected |
| | | | | 10030345 | Oophoritis |
| | | | | 10031064 | Orchitis |
| | | | | 10033119 | Ovarian abscess |
| | | | | 10033847 | Parametritis |
| | | | | 10034236 | Pelvic abscess |
| | | | | 10034254 | Pelvic inflammatory disease |
| | | | | 10034256 | Pelvic inflammatory disease mycoplasmal |
| | | | | 10034294 | Penile abscess |
| | | | | 10036934 | Prostatic abscess |
| | | | | 10036978 | Prostatitis |
| | | | | 10037651 | Pyometra |
| | | | | 10039453 | Salpingitis |
| | | | | 10039748 | Scrotal gangrene |
| | | | | 10039954 | Seminal vesiculitis |

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Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)' | Genital infections (BIcMQ) | 40000004 | | 10044250 | Toxic shock syndrome staphylococcal |
| | | | | 10044251 | Toxic shock syndrome streptococcal |
| | | | | 10046470 | Urethral stricture post infection |
| | | | | 10046914 | Vaginal infection |
| | | | | 10046957 | Vaginitis gardnerella |
| | | | | 10047732 | Vulval abscess |
| | | | | 10047752 | Vulval cellulitis |
| | | | | 10047780 | Vulvitis |
| | | | | 10047784 | Vulvovaginal candidiasis |
| | | | | 10047794 | Vulvovaginitis |
| | | | | 10048461 | Genital infection |
| | | | | 10049205 | Clitoris abscess |
| | | | | 10049571 | Scrotal abscess |
| | | | | 10049573 | Vaginal abscess |
| | | | | 10049677 | Salpingo-oophoritis |
| | | | | 10050428 | Fallopian tube abscess |
| | | | | 10050662 | Prostate infection |
| | | | | 10050739 | Erosive balanitis |
| | | | | 10051458 | Myometritis |
| | | | | 10051483 | Prostatovesiculitis |
| | | | | 10052301 | Vaginal cellulitis |
| | | | | 10052457 | Perineal abscess |
| | | | | 10053043 | Epididymitis ureaplasmal |
| | | | | 10054259 | Escherichia vaginitis |
| | | | | 10054824 | Tubo-ovarian abscess |
| | | | | 10056254 | Intrauterine infection |
| | | | | 10056345 | Rectovaginal septum abscess |
| | | | | 10056628 | Ovarian bacterial infection |
| | | | | 10057001 | Seminal vesicular infection |
| | | | | 10058674 | Pelvic infection |
| | | | | 10059070 | Pelvic sepsis |
| | | | | 10061179 | Genital infection bacterial |
| | | | | 10061180 | Genital infection fungal |
| | | | | 10061182 | Genitourinary tract infection |
| | | | | 10061912 | Penile infection |
| | | | | 10061977 | Genital infection female |
| | | | | 10062156 | Scrotal infection |
| | | | | 10062233 | Uterine infection |
| | | | | 10062316 | Genital abscess |
| | | | | 10062521 | Genital infection male |
| | | | | 10062707 | Parametric abscess |

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Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)' | Genital infections (BIcMQ) | 40000004 | | 10063012 | Uterine abscess |
| | | | | 10064501 | Spermatic cord funiculitis |
| | | | | 10064724 | Testicular abscess |
| | | | | 10064899 | Vulvovaginal mycotic infection |
| | | | | 10064929 | Cellulitis of male external genital organ |
| | | | | 10065583 | Urogenital infection bacterial |
| | | | | 10066876 | Perineal infection |
| | | | | 10067185 | Vulvovaginitis streptococcal |
| | | | | 10067236 | Cervicitis streptococcal |
| | | | | 10067320 | Prostatitis Escherichia coli |
| | | | | 10067741 | Balanoposthitis infective |
| | | | | 10068682 | Gangrenous balanitis |
| | | | | 10069918 | Bacterial prostatitis |
| | | | | 10071209 | Candida cervicitis |
| | | | | 10072020 | Pyospermia |
| | | | | 10074861 | Endometritis bacterial |
| | | | | 10074997 | Mycoplasma genitalium infection |
| | | | | 10075062 | Cervicitis mycoplasmal |
| | | | | 10075620 | Seminal vesicle abscess |
| | | | | 10078662 | Bacterial salpingitis |
| | | | | 10079520 | Vulvovaginitis staphylococcal |
| | | | | 10079521 | Fungal balanitis |
| | | | | 10079528 | Bacterial vulvovaginitis |
| | | | | 10081280 | Ureaplasmal vulvovaginitis |
| | | | | 10082162 | Ureaplasma cervicitis |
| | | | | 10083412 | Neovaginal infection |
| | | | | 10084348 | Scrotal cellulitis |
| | | | | 10085545 | Penile gangrene |
| Narrow BIcMQ 'Ketoacidosis (BIcMQ)' | Events indicative of ketoacidosis (BIcMQ) | 40000008 | | 10012668 | Diabetic hyperglycaemic coma |
| | | | | 10012671 | Diabetic ketoacidosis |
| | | | | 10012672 | Diabetic ketoacidotic hyperglycaemic coma |
| | | | | 10023379 | Ketoacidosis |
| | | | | 10080061 | Euglycaemic diabetic ketoacidosis |
| Narrow BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis' | Pyelonephritis or Urosepsis (BIcMQ) | 40000013 | | 10023424 | Kidney infection |

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Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis' | Pyelonephritis or Urosepsis (BIcMQ) | 40000013 | | 10034531 | Perinephric abscess |
| | | | | 10037584 | Pyelitis |
| | | | | 10037596 | Pyelonephritis |
| | | | | 10037597 | Pyelonephritis acute |
| | | | | 10037601 | Pyelonephritis chronic |
| | | | | 10037603 | Pyelonephritis mycoplasmal |
| | | | | 10037653 | Pyonephrosis |
| | | | | 10038351 | Renal abscess |
| | | | | 10048709 | Urosepsis |
| | | | | 10049100 | Pyelocystitis |
| | | | | 10058596 | Renal cyst infection |
| | | | | 10059517 | Bacterial pyelonephritis |
| | | | | 10065214 | Pyelonephritis fungal |
| | | | | 10068822 | Emphysematous pyelonephritis |
| | | | | 10072058 | Perinephritis |
| | | | | 10074409 | Escherichia pyelonephritis |
| | | | | 10078229 | Renal graft infection |
| | | | | 10082040 | Nephritis bacterial |
| | | | | 10084121 | Infected urinoma |
| Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)' | Urinary tract infections (BIcMQ) | 40000002 | | 10004056 | Bacteriuria |
| | | | | 10004058 | Bacteriuria in pregnancy |
| | | | | 10011781 | Cystitis |
| | | | | 10011790 | Cystitis escherichia |
| | | | | 10011792 | Cystitis gonococcal |
| | | | | 10011793 | Cystitis haemorrhagic |
| | | | | 10011797 | Cystitis klebsiella |
| | | | | 10011799 | Cystitis pseudomonal |
| | | | | 10017525 | Fungal cystitis |
| | | | | 10023424 | Kidney infection |
| | | | | 10034531 | Perinephric abscess |
| | | | | 10037584 | Pyelitis |
| | | | | 10037596 | Pyelonephritis |
| | | | | 10037597 | Pyelonephritis acute |
| | | | | 10037601 | Pyelonephritis chronic |
| | | | | 10037603 | Pyelonephritis mycoplasmal |
| | | | | 10037653 | Pyonephrosis |
| | | | | 10038351 | Renal abscess |
| | | | | 10046424 | Urethral abscess |
| | | | | 10046470 | Urethral stricture post infection |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)' | Urinary tract infections (BIcMQ) | 40000002 | | 10046480 | Urethritis |
| | | | | 10046482 | Urethritis chlamydial |
| | | | | 10046483 | Urethritis gonococcal |
| | | | | 10046489 | Urethritis trichomonal |
| | | | | 10046490 | Urethritis ureaplasmal |
| | | | | 10046571 | Urinary tract infection |
| | | | | 10046572 | Urinary tract infection enterococcal |
| | | | | 10046573 | Urinary tract infection neonatal |
| | | | | 10046704 | Urogenital trichomoniasis |
| | | | | 10048709 | Urosepsis |
| | | | | 10049059 | Urinary tract infection fungal |
| | | | | 10049100 | Pyelocystitis |
| | | | | 10051250 | Ureteritis |
| | | | | 10051959 | Urinary bladder abscess |
| | | | | 10052238 | Escherichia urinary tract infection |
| | | | | 10052299 | Urethral carbuncle |
| | | | | 10054088 | Urinary tract infection bacterial |
| | | | | 10056351 | Emphysematous cystitis |
| | | | | 10056396 | Asymptomatic bacteriuria |
| | | | | 10058523 | Bladder candidiasis |
| | | | | 10058596 | Renal cyst infection |
| | | | | 10059517 | Bacterial pyelonephritis |
| | | | | 10061181 | Genitourinary tract gonococcal infection |
| | | | | 10061395 | Ureter abscess |
| | | | | 10062279 | Urinary tract infection pseudomonal |
| | | | | 10062280 | Urinary tract infection staphylococcal |
| | | | | 10064850 | Cystitis erosive |
| | | | | 10065198 | Cystitis bacterial |
| | | | | 10065214 | Pyelonephritis fungal |
| | | | | 10065582 | Urogenital infection fungal |
| | | | | 10065583 | Urogenital infection bacterial |
| | | | | 10066757 | Urinary tract abscess |
| | | | | 10068822 | Emphysematous pyelonephritis |
| | | | | 10070300 | Streptococcal urinary tract infection |
| | | | | 10072058 | Perinephritis |
| | | | | 10074409 | Escherichia pyelonephritis |
| | | | | 10074457 | Bladder diverticulitis |
| | | | | 10075063 | Urethritis mycoplasmal |
| | | | | 10077375 | Funguria |
| | | | | 10078229 | Renal graft infection |
| | | | | 10078665 | Bacterial urethritis |

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Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)' | Urinary tract infections (BIcMQ) | 40000002 | | 10078666 | Bacterial ureteritis |
| | | | | 10081163 | Fungal urethritis |
| | | | | 10081185 | Gonococcal infection |
| | | | | 10081262 | Candida urethritis |
| | | | | 10082040 | Nephritis bacterial |
| | | | | 10082818 | Providencia urinary tract infection |
| | | | | 10083162 | Urinary tract candidiasis |
| | | | | 10083524 | Campylobacter urinary tract infection |
| | | | | 10084121 | Infected urinoma |
| | | | | 10084826 | Aerococcus urinae infection |
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)' | Volume depletion events (BIcMQ) | 40000006 | | 10005731 | Blood pressure ambulatory decreased |
| | | | | 10005734 | Blood pressure decreased |
| | | | | 10005737 | Blood pressure diastolic decreased |
| | | | | 10005758 | Blood pressure systolic decreased |
| | | | | 10009192 | Circulatory collapse |
| | | | | 10012174 | Dehydration |
| | | | | 10021097 | Hypotension |
| | | | | 10021137 | Hypovolaemia |
| | | | | 10021138 | Hypovolaemic shock |
| | | | | 10026983 | Mean arterial pressure decreased |
| | | | | 10031127 | Orthostatic hypotension |
| | | | | 10036653 | Presyncope |
| | | | | 10042772 | Syncope |
| | | | | 10053356 | Blood pressure orthostatic decreased |
| | | | | 10066077 | Diastolic hypotension |
| | | | | 10078280 | CT hypotension complex |
| | | | | 10083659 | Hypotensive crisis |
| | | | | 10084012 | Dialysis hypotension |
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)' excluding PTs 'Dehydration' and 'Hypovolaemia' | Hypotension events (BIcMQ) | 40000001 | | 10005731 | Blood pressure ambulatory decreased |
| | | | | 10005734 | Blood pressure decreased |
| | | | | 10005737 | Blood pressure diastolic decreased |
| | | | | 10005758 | Blood pressure systolic decreased |
| | | | | 10009192 | Circulatory collapse |
| | | | | 10021097 | Hypotension |
| | | | | 10021138 | Hypovolaemic shock |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)' excluding PTs 'Dehydration' and 'Hypovolaemia' | Hypotension events (BIcMQ) | 40000001 | | 10026983 | Mean arterial pressure decreased |
| | | | | 10031127 | Orthostatic hypotension |
| | | | | 10036653 | Presyncope |
| | | | | 10042772 | Syncope |
| | | | | 10053356 | Blood pressure orthostatic decreased |
| | | | | 10066077 | Diastolic hypotension |
| | | | | 10078280 | CT hypotension complex |
| | | | | 10083659 | Hypotensive crisis |
| | | | | 10084012 | Dialysis hypotension |
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10000804 | Acute hepatic failure |
| | | | | 10001547 | Alanine aminotransferase abnormal |
| | | | | 10001551 | Alanine aminotransferase increased |
| | | | | 10001942 | Ammonia abnormal |
| | | | | 10001946 | Ammonia increased |
| | | | | 10003445 | Ascites |
| | | | | 10003477 | Aspartate aminotransferase abnormal |
| | | | | 10003481 | Aspartate aminotransferase increased |
| | | | | 10003547 | Asterixis |
| | | | | 10003827 | Autoimmune hepatitis |
| | | | | 10004659 | Biliary cirrhosis |
| | | | | 10004664 | Biliary fibrosis |
| | | | | 10004685 | Bilirubin conjugated increased |
| | | | | 10004792 | Biopsy liver abnormal |
| | | | | 10005364 | Blood bilirubin increased |
| | | | | 10005370 | Blood bilirubin unconjugated increased |
| | | | | 10006408 | Bromosulphthalein test abnormal |
| | | | | 10008635 | Cholestasis |
| | | | | 10008909 | Chronic hepatitis |
| | | | | 10010075 | Coma hepatic |
| | | | | 10017688 | Gamma-glutamyltransferase abnormal |
| | | | | 10017693 | Gamma-glutamyltransferase increased |
| | | | | 10019621 | Hepaplastin abnormal |
| | | | | 10019622 | Hepaplastin decreased |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10019637 | Hepatic atrophy |
| | | | | 10019641 | Hepatic cirrhosis |
| | | | | 10019660 | Hepatic encephalopathy |
| | | | | 10019663 | Hepatic failure |
| | | | | 10019668 | Hepatic fibrosis |
| | | | | 10019670 | Hepatic function abnormal |
| | | | | 10019692 | Hepatic necrosis |
| | | | | 10019705 | Hepatic pain |
| | | | | 10019708 | Hepatic steatosis |
| | | | | 10019717 | Hepatitis |
| | | | | 10019727 | Hepatitis acute |
| | | | | 10019754 | Hepatitis cholestatic |
| | | | | 10019755 | Hepatitis chronic active |
| | | | | 10019759 | Hepatitis chronic persistent |
| | | | | 10019772 | Hepatitis fulminant |
| | | | | 10019795 | Hepatitis toxic |
| | | | | 10019837 | Hepatocellular injury |
| | | | | 10019842 | Hepatomegaly |
| | | | | 10019845 | Hepatorenal failure |
| | | | | 10019846 | Hepatorenal syndrome |
| | | | | 10019847 | Hepatosplenomegaly |
| | | | | 10019851 | Hepatotoxicity |
| | | | | 10020575 | Hyperammonaemia |
| | | | | 10020578 | Hyperbilirubinaemia |
| | | | | 10021209 | Icterus index increased |
| | | | | 10023025 | Ischaemic hepatitis |
| | | | | 10023126 | Jaundice |
| | | | | 10023129 | Jaundice cholestatic |
| | | | | 10023136 | Jaundice hepatocellular |
| | | | | 10023321 | Kayser-Fleischer ring |
| | | | | 10024670 | Liver disorder |
| | | | | 10024690 | Liver function test abnormal |
| | | | | 10024712 | Liver tenderness |
| | | | | 10024714 | Liver transplant |
| | | | | 10025129 | Lupoid hepatic cirrhosis |
| | | | | 10029530 | Non-alcoholic fatty liver |
| | | | | 10030210 | Oesophageal varices haemorrhage |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10036200 | Portal hypertension |
| | | | | 10039012 | Reye's syndrome |
| | | | | 10045428 | Ultrasound liver abnormal |
| | | | | 10048611 | Cholaemia |
| | | | | 10049199 | Hepatic cytolysis |
| | | | | 10049631 | Oedema due to hepatic disease |
| | | | | 10050792 | Urine bilirubin increased |
| | | | | 10050897 | Portal hypertensive gastropathy |
| | | | | 10051010 | Duodenal varices |
| | | | | 10051012 | Gastric varices |
| | | | | 10051015 | Radiation hepatitis |
| | | | | 10051081 | Nodular regenerative hyperplasia |
| | | | | 10051333 | Guanase increased |
| | | | | 10051343 | Bile output decreased |
| | | | | 10051344 | Bile output abnormal |
| | | | | 10051924 | Hypercholia |
| | | | | 10052274 | Hepatopulmonary syndrome |
| | | | | 10052279 | Renal and liver transplant |
| | | | | 10052550 | Liver induration |
| | | | | 10052554 | Foetor hepaticus |
| | | | | 10053219 | Non-alcoholic steatohepatitis |
| | | | | 10053244 | Hepatocellular foamy cell syndrome |
| | | | | 10054125 | Perihepatic discomfort |
| | | | | 10054889 | Transaminases increased |
| | | | | 10056091 | Varices oesophageal |
| | | | | 10056536 | X-ray hepatobiliary abnormal |
| | | | | 10056956 | Subacute hepatic failure |
| | | | | 10057110 | Hepatic mass |
| | | | | 10057572 | Gastric varices haemorrhage |
| | | | | 10057573 | Chronic hepatic failure |
| | | | | 10058117 | Ocular icterus |
| | | | | 10058477 | Blood bilirubin abnormal |
| | | | | 10059710 | Galactose elimination capacity test abnormal |
| | | | | 10059712 | Galactose elimination capacity test decreased |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10060107 | Liver-kidney microsomal antibody positive |
| | | | | 10060794 | Hepatic enzyme decreased |
| | | | | 10060795 | Hepatic enzyme increased |
| | | | | 10061009 | Bilirubin excretion disorder |
| | | | | 10061135 | Spontaneous bacterial peritonitis |
| | | | | 10061947 | Liver scan abnormal |
| | | | | 10061997 | Hepatectomy |
| | | | | 10061998 | Hepatic lesion |
| | | | | 10062000 | Hepatobiliary disease |
| | | | | 10062040 | Liver operation |
| | | | | 10062685 | Hepatic enzyme abnormal |
| | | | | 10062688 | Transaminases abnormal |
| | | | | 10063075 | Cryptogenic cirrhosis |
| | | | | 10064190 | Cholestatic pruritus |
| | | | | 10064558 | Total bile acids increased |
| | | | | 10064668 | Hepatic infiltration eosinophilic |
| | | | | 10064676 | Graft versus host disease in liver |
| | | | | 10064712 | Mitochondrial aspartate aminotransferase increased |
| | | | | 10065274 | Hepatic calcification |
| | | | | 10066195 | Hepatobiliary scan abnormal |
| | | | | 10066244 | Hepatic sequestration |
| | | | | 10066263 | Acute graft versus host disease in liver |
| | | | | 10066597 | Gastrooesophageal variceal haemorrhage prophylaxis |
| | | | | 10066599 | Hepatic encephalopathy prophylaxis |
| | | | | 10066758 | Mixed liver injury |
| | | | | 10066869 | Molar ratio of total branched-chain amino acid to tyrosine |
| | | | | 10067125 | Liver injury |
| | | | | 10067281 | Portopulmonary hypertension |
| | | | | 10067338 | Retrograde portal vein flow |
| | | | | 10067365 | Hepatic hydrothorax |
| | | | | 10067718 | Bilirubin conjugated abnormal |
| | | | | 10067737 | Lupus hepatitis |
| | | | | 10067823 | Splenic varices |
| | | | | 10067969 | Cholestatic liver injury |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10068237 | Hypertransaminasaemia |
| | | | | 10068287 | Child-Pugh-Turcotte score increased |
| | | | | 10068358 | Hepatic vascular resistance increased |
| | | | | 10068547 | Bacterascites |
| | | | | 10068662 | Splenic varices haemorrhage |
| | | | | 10068923 | Portal hypertensive enteropathy |
| | | | | 10068997 | Hepatic artery flow decreased |
| | | | | 10070815 | Acute yellow liver atrophy |
| | | | | 10070953 | Reynold's syndrome |
| | | | | 10071198 | Allergic hepatitis |
| | | | | 10071265 | Diabetic hepatopathy |
| | | | | 10071502 | Intestinal varices |
| | | | | 10072160 | Chronic graft versus host disease in liver |
| | | | | 10072268 | Drug-induced liver injury |
| | | | | 10072284 | Varicose veins of abdominal wall |
| | | | | 10072319 | Gallbladder varices |
| | | | | 10073209 | Portal vein dilatation |
| | | | | 10073215 | Peripancreatic varices |
| | | | | 10073979 | Portal vein cavernous transformation |
| | | | | 10074150 | Biliary ascites |
| | | | | 10074151 | Parenteral nutrition associated liver disease |
| | | | | 10074726 | Portal fibrosis |
| | | | | 10075895 | Liver palpable |
| | | | | 10076237 | Gastric variceal injection |
| | | | | 10076238 | Gastric variceal ligation |
| | | | | 10076254 | Hepatic hypertrophy |
| | | | | 10076331 | Steatohepatitis |
| | | | | 10076640 | Liver dialysis |
| | | | | 10077020 | Child-Pugh-Turcotte score abnormal |
| | | | | 10077215 | Hepatic steato-fibrosis |
| | | | | 10077259 | Non-cirrhotic portal hypertension |
| | | | | 10077305 | Acute on chronic liver failure |
| | | | | 10077356 | Bilirubin urine present |
| | | | | 10077677 | Liver function test decreased |
| | | | | 10077692 | Liver function test increased |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BICMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10078058 | Intestinal varices haemorrhage |
| | | | | 10078360 | Computerised tomogram liver abnormal |
| | | | | 10078438 | White nipple sign |
| | | | | 10078962 | Immune-mediated hepatitis |
| | | | | 10079446 | Portal hypertensive colopathy |
| | | | | 10080429 | Primary biliary cholangitis |
| | | | | 10080576 | Alloimmune hepatitis |
| | | | | 10080679 | Regenerative siderotic hepatic nodule |
| | | | | 10080860 | Acquired hepatocerebral degeneration |
| | | | | 10082443 | Magnetic resonance proton density fat fraction measurement |
| | | | | 10082480 | Cardiohepatic syndrome |
| | | | | 10082832 | AST/ALT ratio abnormal |
| | | | | 10083010 | Sugiura procedure |
| | | | | 10083171 | Hepatic venous pressure gradient increased |
| | | | | 10083172 | Hepatic venous pressure gradient abnormal |
| | | | | 10083406 | Immune-mediated cholangitis |
| | | | | 10083521 | Immune-mediated hepatic disorder |
| | | | | 10084058 | Congestive hepatopathy |
| | | | | 10084751 | Hepatic hypoperfusion |
| | | | | 10084797 | Flood syndrome |
| | | | | 10085121 | Magnetic resonance imaging hepatobiliary abnormal |
| | | | | 10086006 | Acquired factor V deficiency |
| | | | | 10086970 | Anti-liver cytosol antibody type 1 positive |
| | | | | 10087030 | Omental oedema |
| PTs 'Gout', 'Gouty arthritis', 'Gouty tophus' | Gout (user-defined) | 40000032 | | 10018627 | Gout |
| | | | | 10018634 | Gouty arthritis |
| | | | | 10018641 | Gouty tophus |
| PTs 'Hyperkalaemia', 'Blood potassium increased' | Hyperkalaemia (user-defined) | 40000021 | | 10005725 | Blood potassium increased |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.3.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BICMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| PTs 'Hyperkalaemia', 'Blood potassium increased' | Hyperkalaemia (user-defined) | 40000021 | | 10020646 | Hyperkalaemia |
| SMQ 'Acute renal failure' | Acute renal failure (SMQ) | 20000003 | Narrow | 10002847 | Anuria |
| | | | | 10003885 | Azotaemia |
| | | | | 10018875 | Haemodialysis |
| | | | | 10029155 | Nephropathy toxic |
| | | | | 10030302 | Oliguria |
| | | | | 10034660 | Peritoneal dialysis |
| | | | | 10038435 | Renal failure |
| | | | | 10038447 | Renal failure neonatal |
| | | | | 10049776 | Renal impairment neonatal |
| | | | | 10049778 | Neonatal anuria |
| | | | | 10053090 | Haemofiltration |
| | | | | 10061105 | Dialysis |
| | | | | 10062237 | Renal impairment |
| | | | | 10066338 | Continuous haemodiafiltration |
| | | | | 10069339 | Acute kidney injury |
| | | | | 10069688 | Acute phosphate nephropathy |
| | | | | 10072370 | Prerenal failure |
| | | | | 10078987 | Foetal renal impairment |
| | | | | 10081980 | Subacute kidney injury |
| SMQ 'Hypoglycaemia' | Hypoglycaemic events (SMQ) | 20000226 | Narrow | 10005555 | Blood glucose decreased |
| | | | | 10020993 | Hypoglycaemia |
| | | | | 10020994 | Hypoglycaemia neonatal |
| | | | | 10020997 | Hypoglycaemia unawareness |
| | | | | 10021000 | Hypoglycaemic coma |
| | | | | 10021002 | Hypoglycaemic encephalopathy |
| | | | | 10040576 | Shock hypoglycaemic |
| | | | | 10048803 | Hypoglycaemic seizure |
| | | | | 10054998 | Neuroglycopenia |
| | | | | 10059035 | Postprandial hypoglycaemia |
| | | | | 10065981 | Hypoglycaemic unconsciousness |
| | | | | 10077216 | Hyperinsulinaemic hypoglycaemia |
| | | | | 10080024 | Nesidioblastosis |
| | | | | 10082152 | Paraneoplastic hypoglycaemia |
| | | | | 10082172 | Glycopenia |

Analyses are based on 1245.121 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

**R.4**

**R.4.1**

**R.4.1.1**

**R.4.1.1.1**

R.4.1.1.1.1 Time to all-cause mortality

Table R.4.1.1.1.1: 1 Cox Regression for time to all-cause mortality overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1188 | 132 | 11.1 | 3.86 | 1171 | 92 | 7.9 | 2.68 | 0.70 | (0.53,0.91) | 0.0081 | |
| Sex | | | | | | | | | | | | 0.0367 |
| Male | 864 | 108 | 12.5 | 4.34 | 837 | 62 | 7.4 | 2.54 | 0.59 | (0.43,0.81) | 0.0010 | |
| Female | 324 | 24 | 7.4 | 2.58 | 334 | 30 | 9.0 | 3.05 | 1.15 | (0.67,1.96) | 0.6177 | |
| Age [years] | | | | | | | | | | | | 0.4907 |
| <65 | 569 | 51 | 9.0 | 3.07 | 547 | 31 | 5.7 | 1.88 | 0.61 | (0.39,0.95) | 0.0298 | |
| >=65 | 619 | 81 | 13.1 | 4.61 | 624 | 61 | 9.8 | 3.44 | 0.74 | (0.53,1.03) | 0.0781 | |
| Region | | | | | | | | | | | | 0.2805 |
| Europe | 468 | 52 | 11.1 | 3.86 | 434 | 42 | 9.7 | 3.38 | 0.88 | (0.59,1.33) | 0.5554 | |
| North America | 259 | 23 | 8.9 | 3.03 | 241 | 17 | 7.1 | 2.38 | 0.81 | (0.43,1.51) | 0.5009 | |
| Latin America | 177 | 25 | 14.1 | 5.11 | 191 | 18 | 9.4 | 3.29 | 0.61 | (0.33,1.11) | 0.1068 | |
| Africa | 50 | 4 | 8.0 | 2.80 | 54 | 4 | 7.4 | 2.63 | 0.84 | (0.21,3.36) | 0.8032 | |
| Asia | 234 | 28 | 12.0 | 4.11 | 251 | 11 | 4.4 | 1.43 | 0.37 | (0.18,0.73) | 0.0047 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0979 |
| <30 | 554 | 77 | 13.9 | 4.85 | 566 | 45 | 8.0 | 2.71 | 0.57 | (0.39,0.82) | 0.0025 | |
| >=30 | 634 | 55 | 8.7 | 3.00 | 605 | 47 | 7.8 | 2.67 | 0.89 | (0.60,1.31) | 0.5575 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5736 |
| <130 | 379 | 46 | 12.1 | 4.22 | 382 | 28 | 7.3 | 2.48 | 0.62 | (0.39,1.00) | 0.0507 | |
| >=130 | 809 | 86 | 10.6 | 3.69 | 789 | 64 | 8.1 | 2.79 | 0.74 | (0.53,1.02) | 0.0646 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4719 |
| <75 | 500 | 59 | 11.8 | 4.06 | 500 | 41 | 8.2 | 2.76 | 0.69 | (0.46,1.03) | 0.0686 | |
| 75 to <85 | 427 | 47 | 11.0 | 3.86 | 417 | 28 | 6.7 | 2.30 | 0.59 | (0.37,0.94) | 0.0259 | |
| >=85 | 261 | 26 | 10.0 | 3.48 | 254 | 23 | 9.1 | 3.16 | 0.93 | (0.53,1.63) | 0.7907 | |
| History of heart failure | | | | | | | | | | | | 0.1731 |
| No | 1048 | 109 | 10.4 | 3.58 | 1031 | 70 | 6.8 | 2.29 | 0.64 | (0.47,0.86) | 0.0032 | |
| Yes | 140 | 23 | 16.4 | 6.10 | 140 | 22 | 15.7 | 6.00 | 1.01 | (0.56,1.81) | 0.9822 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2761 |
| <45 | 179 | 27 | 15.1 | 5.27 | 178 | 23 | 12.9 | 4.56 | 0.92 | (0.53,1.61) | 0.7807 | |
| >=45 | 1009 | 105 | 10.4 | 3.61 | 993 | 69 | 6.9 | 2.36 | 0.65 | (0.48,0.88) | 0.0053 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.4.1.1.1.1: 1 Cox Regression for time to all-cause mortality overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2935 |
| Normal (<30) | 250 | 24 | 9.6 | 3.21 | 257 | 23 | 8.9 | 3.02 | 0.97 | (0.54,1.71) | 0.9077 | |
| Microalbuminuria (30 to <=300) | 675 | 67 | 9.9 | 3.43 | 645 | 36 | 5.6 | 1.90 | 0.56 | (0.37,0.84) | 0.0051 | |
| Macroalbuminuria (>300) | 260 | 41 | 15.8 | 5.78 | 261 | 33 | 12.6 | 4.44 | 0.75 | (0.47,1.18) | 0.2121 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0875 |
| Low, moderate or high | 1018 | 105 | 10.3 | 3.57 | 1001 | 64 | 6.4 | 2.17 | 0.61 | (0.45,0.84) | 0.0021 | |
| Very high | 167 | 27 | 16.2 | 5.77 | 162 | 28 | 17.3 | 6.22 | 1.05 | (0.62,1.78) | 0.8649 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.3665 |
| No | 205 | 25 | 12.2 | 4.15 | 211 | 14 | 6.6 | 2.21 | 0.53 | (0.28,1.02) | 0.0579 | |
| Yes | 983 | 107 | 10.9 | 3.80 | 960 | 78 | 8.1 | 2.79 | 0.74 | (0.55,0.99) | 0.0420 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4563 |
| No | 422 | 50 | 11.8 | 4.17 | 408 | 31 | 7.6 | 2.61 | 0.61 | (0.39,0.95) | 0.0302 | |
| Yes | 766 | 82 | 10.7 | 3.69 | 763 | 61 | 8.0 | 2.73 | 0.75 | (0.54,1.05) | 0.0934 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3262 |
| No | 629 | 61 | 9.7 | 3.34 | 589 | 36 | 6.1 | 2.05 | 0.59 | (0.39,0.90) | 0.0135 | |
| Yes | 559 | 71 | 12.7 | 4.45 | 582 | 56 | 9.6 | 3.36 | 0.78 | (0.55,1.11) | 0.1650 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.1.1: 1**

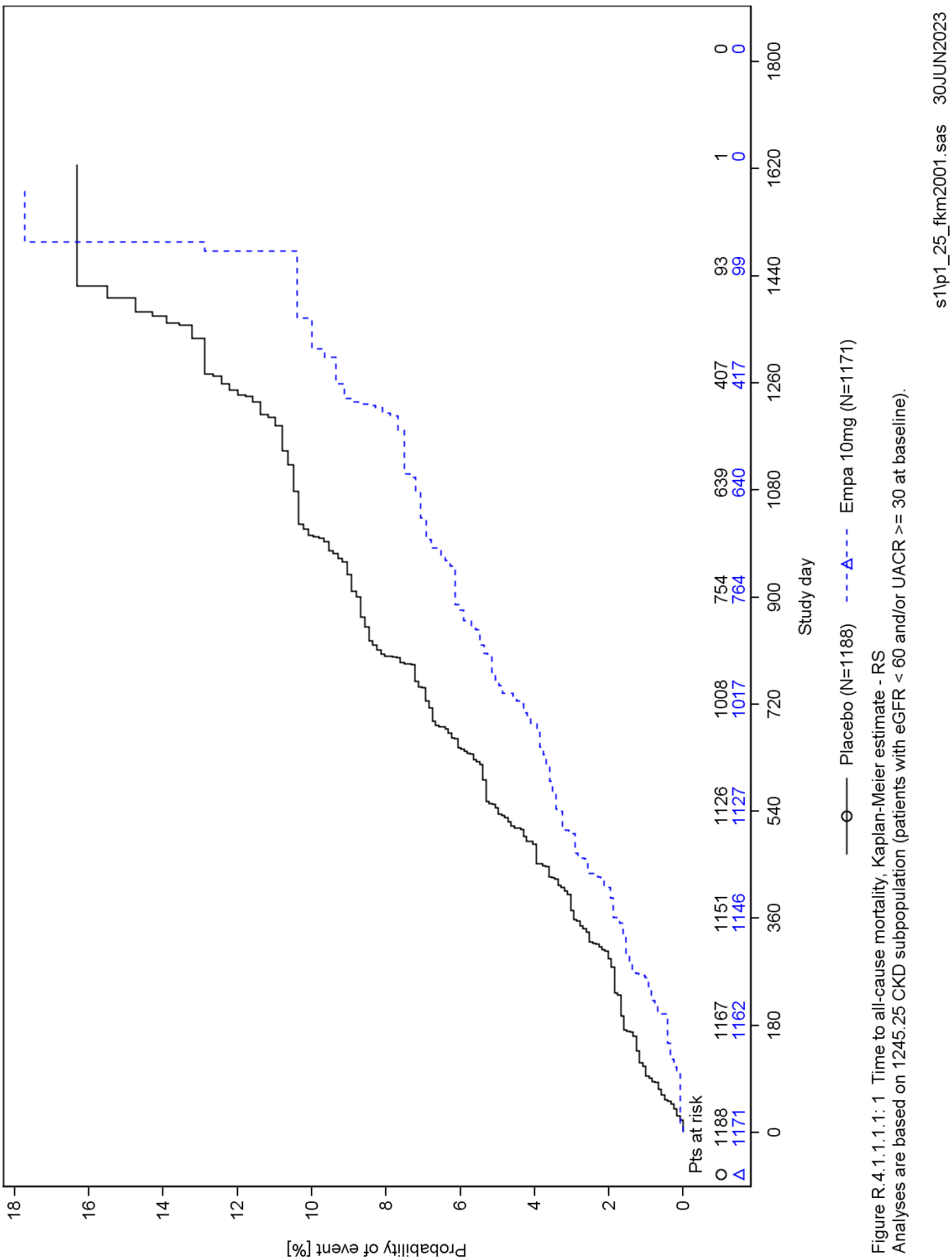


Figure R.4.1.1.1.1: 1 Time to all-cause mortality, Kaplan-Meier estimate - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.1.1: 2**

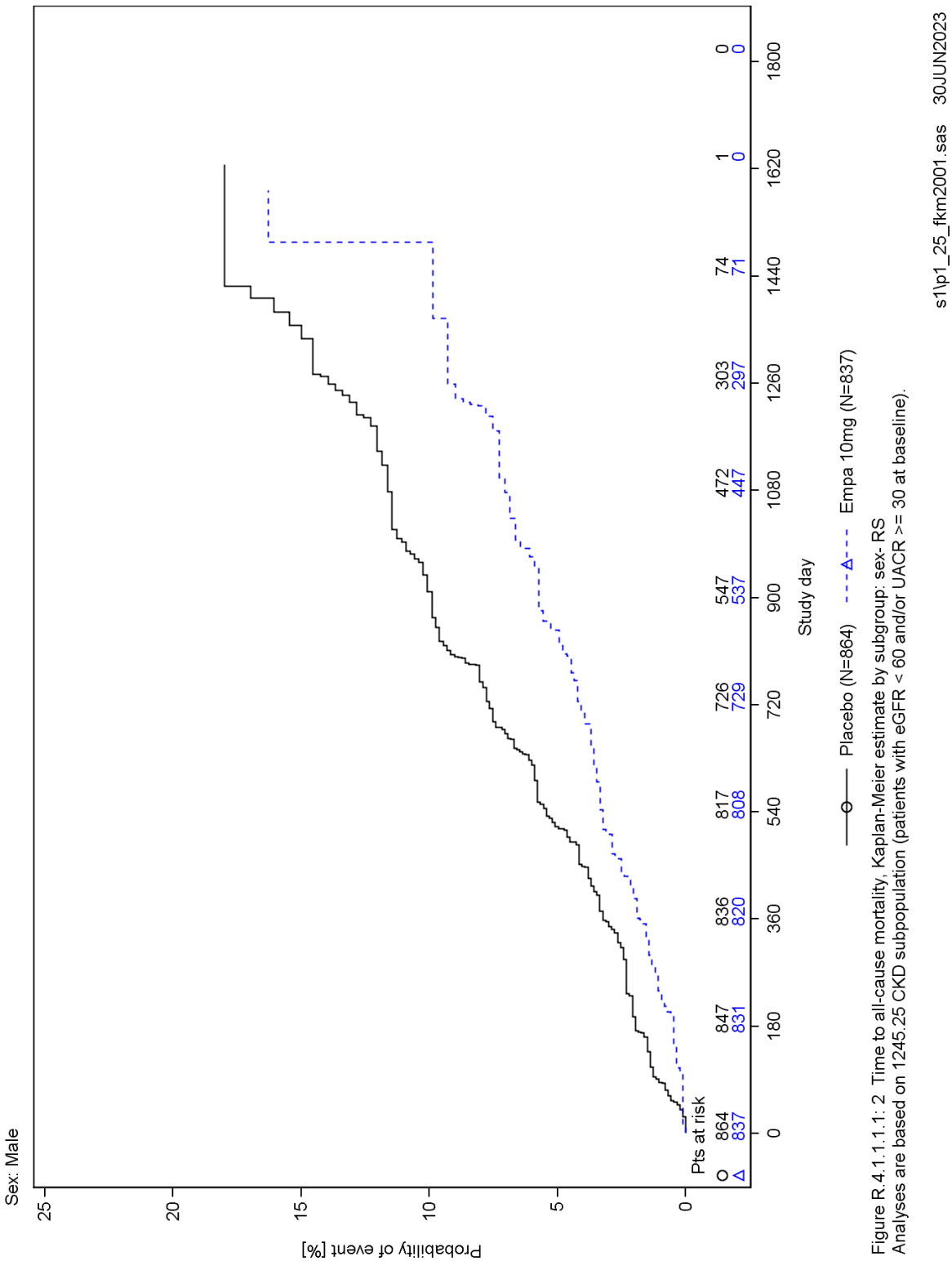


Figure R.4.1.1.1.1: 2 Time to all-cause mortality, Kaplan-Meier estimate by subgroup: sex- RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.1.1: 2**

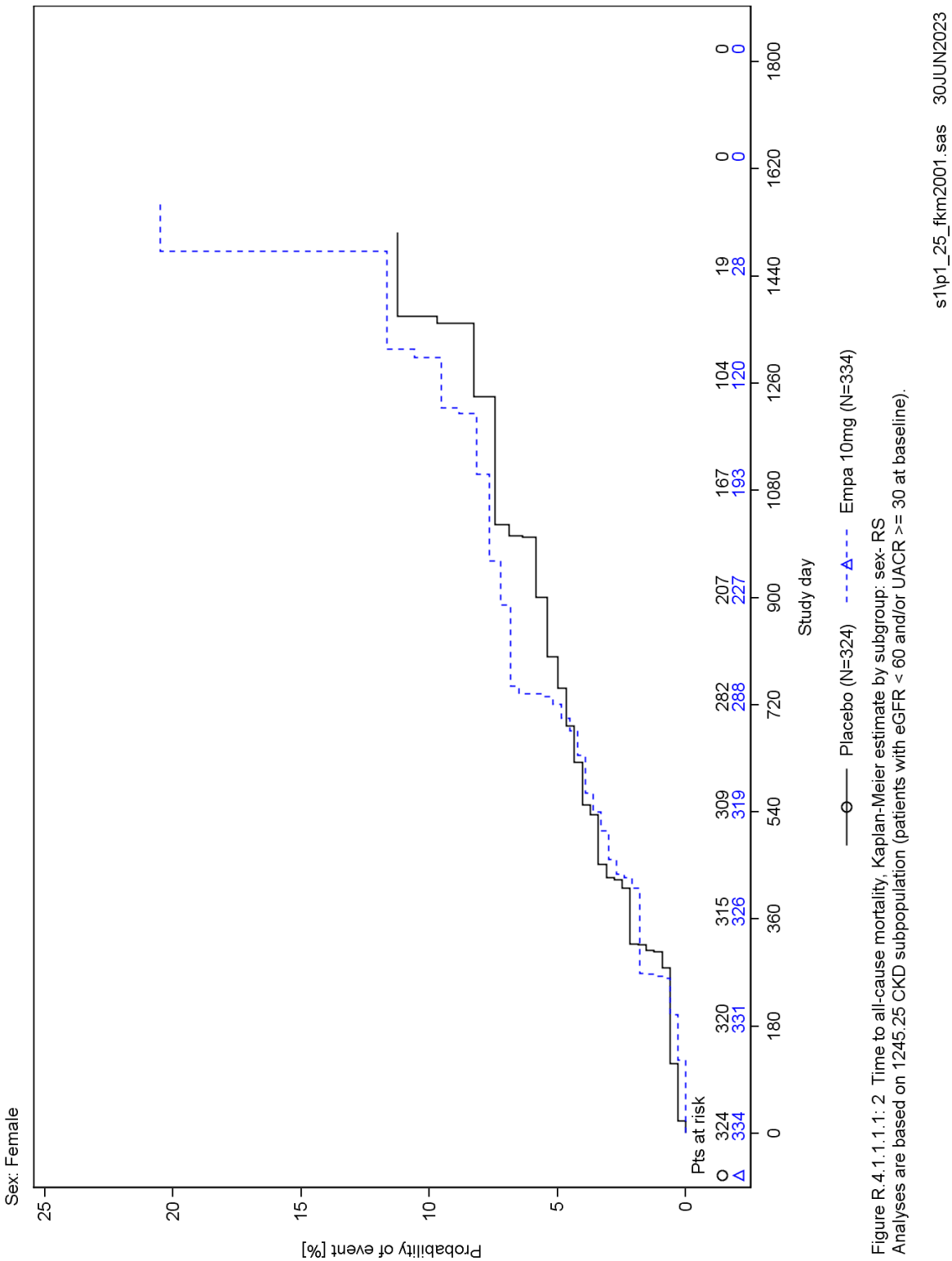


Figure R.4.1.1.1.1: 2 Time to all-cause mortality, Kaplan-Meier estimate by subgroup: sex- RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.4.1.1.1.2**

R.4.1.1.1.2 Time to adjudicated CV death

Table R.4.1.1.1.2: 1 Cox Regression for time to adjudicated CV death overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 97 | 8.2 | 2.84 | 1171 | 58 | 5.0 | 1.69 | 0.59 | (0.43,0.82) | 0.0017 | |
| Sex | | | | | | | | | | | | 0.2236 |
| Male | 864 | 77 | 8.9 | 3.09 | 837 | 40 | 4.8 | 1.64 | 0.53 | (0.36,0.77) | 0.0010 | |
| Female | 324 | 20 | 6.2 | 2.15 | 334 | 18 | 5.4 | 1.83 | 0.84 | (0.44,1.58) | 0.5810 | |
| Age [years] | | | | | | | | | | | | 0.9964 |
| <65 | 569 | 42 | 7.4 | 2.53 | 547 | 25 | 4.6 | 1.51 | 0.59 | (0.36,0.97) | 0.0379 | |
| >=65 | 619 | 55 | 8.9 | 3.13 | 624 | 33 | 5.3 | 1.86 | 0.59 | (0.38,0.91) | 0.0177 | |
| Region | | | | | | | | | | | | 0.3029 |
| Europe | 468 | 36 | 7.7 | 2.67 | 434 | 28 | 6.5 | 2.25 | 0.84 | (0.51,1.38) | 0.4877 | |
| North America | 259 | 16 | 6.2 | 2.11 | 241 | 9 | 3.7 | 1.26 | 0.62 | (0.28,1.41) | 0.2583 | |
| Latin America | 177 | 19 | 10.7 | 3.89 | 191 | 12 | 6.3 | 2.19 | 0.54 | (0.26,1.12) | 0.0965 | |
| Africa | 50 | 4 | 8.0 | 2.80 | 54 | 2 | 3.7 | 1.31 | 0.44 | (0.08,2.40) | 0.3415 | |
| Asia | 234 | 22 | 9.4 | 3.23 | 251 | 7 | 2.8 | 0.91 | 0.29 | (0.12,0.67) | 0.0041 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1931 |
| <30 | 554 | 57 | 10.3 | 3.59 | 566 | 29 | 5.1 | 1.74 | 0.49 | (0.31,0.76) | 0.0016 | |
| >=30 | 634 | 40 | 6.3 | 2.18 | 605 | 29 | 4.8 | 1.64 | 0.75 | (0.47,1.21) | 0.2436 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7393 |
| <130 | 379 | 31 | 8.2 | 2.84 | 382 | 17 | 4.5 | 1.50 | 0.55 | (0.30,0.99) | 0.0451 | |
| >=130 | 809 | 66 | 8.2 | 2.83 | 789 | 41 | 5.2 | 1.79 | 0.62 | (0.42,0.91) | 0.0148 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.1561 |
| <75 | 500 | 40 | 8.0 | 2.75 | 500 | 26 | 5.2 | 1.75 | 0.64 | (0.39,1.05) | 0.0748 | |
| 75 to <85 | 427 | 38 | 8.9 | 3.12 | 417 | 15 | 3.6 | 1.23 | 0.39 | (0.21,0.71) | 0.0020 | |
| >=85 | 261 | 19 | 7.3 | 2.54 | 254 | 17 | 6.7 | 2.34 | 0.92 | (0.48,1.77) | 0.8052 | |
| History of heart failure | | | | | | | | | | | | 0.2152 |
| No | 1048 | 80 | 7.6 | 2.63 | 1031 | 44 | 4.3 | 1.44 | 0.54 | (0.37,0.78) | 0.0010 | |
| Yes | 140 | 17 | 12.1 | 4.51 | 140 | 14 | 10.0 | 3.82 | 0.89 | (0.44,1.82) | 0.7536 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6331 |
| <45 | 179 | 17 | 9.5 | 3.32 | 178 | 11 | 6.2 | 2.18 | 0.71 | (0.33,1.51) | 0.3692 | |
| >=45 | 1009 | 80 | 7.9 | 2.75 | 993 | 47 | 4.7 | 1.61 | 0.57 | (0.40,0.82) | 0.0026 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.4.1.1.1.2: 1 Cox Regression for time to adjudicated CV death overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0280 |
| Normal (<30) | 250 | 12 | 4.8 | 1.60 | 257 | 17 | 6.6 | 2.23 | 1.42 | (0.68,2.98) | 0.3529 | |
| Microalbuminuria (30 to <=300) | 675 | 49 | 7.3 | 2.51 | 645 | 20 | 3.1 | 1.05 | 0.42 | (0.25,0.70) | 0.0010 | |
| Macroalbuminuria (>300) | 260 | 36 | 13.8 | 5.08 | 261 | 21 | 8.0 | 2.83 | 0.55 | (0.32,0.95) | 0.0314 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4924 |
| Low, moderate or high | 1018 | 76 | 7.5 | 2.58 | 1001 | 43 | 4.3 | 1.46 | 0.56 | (0.39,0.82) | 0.0026 | |
| Very high | 167 | 21 | 12.6 | 4.49 | 162 | 15 | 9.3 | 3.33 | 0.73 | (0.38,1.42) | 0.3607 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7464 |
| No | 205 | 16 | 7.8 | 2.66 | 211 | 9 | 4.3 | 1.42 | 0.52 | (0.23,1.19) | 0.1221 | |
| Yes | 983 | 81 | 8.2 | 2.87 | 960 | 49 | 5.1 | 1.75 | 0.61 | (0.43,0.87) | 0.0060 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.7772 |
| No | 422 | 37 | 8.8 | 3.09 | 408 | 21 | 5.1 | 1.77 | 0.56 | (0.33,0.95) | 0.0331 | |
| Yes | 766 | 60 | 7.8 | 2.70 | 763 | 37 | 4.8 | 1.65 | 0.62 | (0.41,0.93) | 0.0203 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.8124 |
| No | 629 | 37 | 5.9 | 2.03 | 589 | 23 | 3.9 | 1.31 | 0.62 | (0.37,1.04) | 0.0712 | |
| Yes | 559 | 60 | 10.7 | 3.76 | 582 | 35 | 6.0 | 2.10 | 0.57 | (0.38,0.87) | 0.0085 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.1.2: 1**

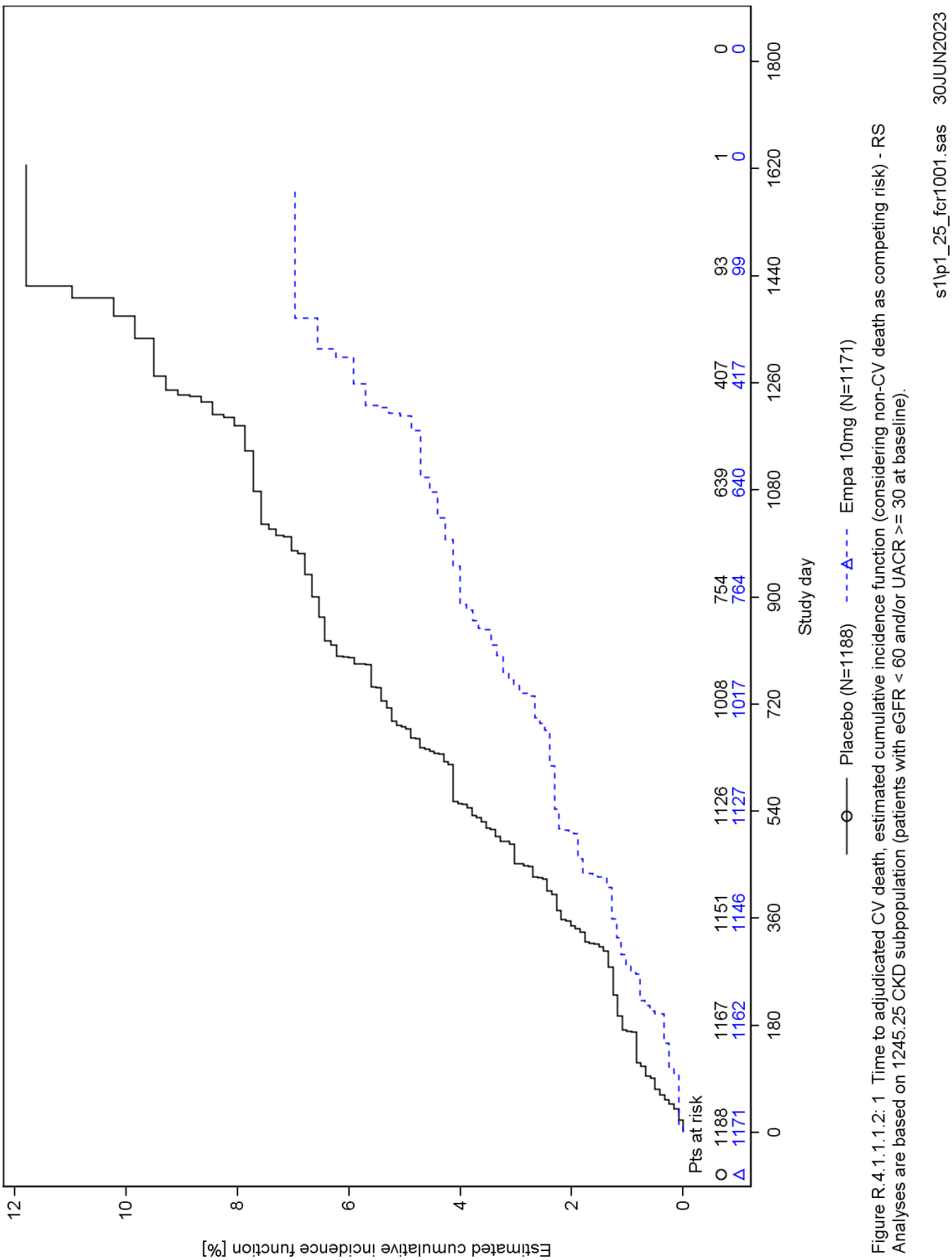


Figure R.4.1.1.1.2: 1 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.1.2: 2**

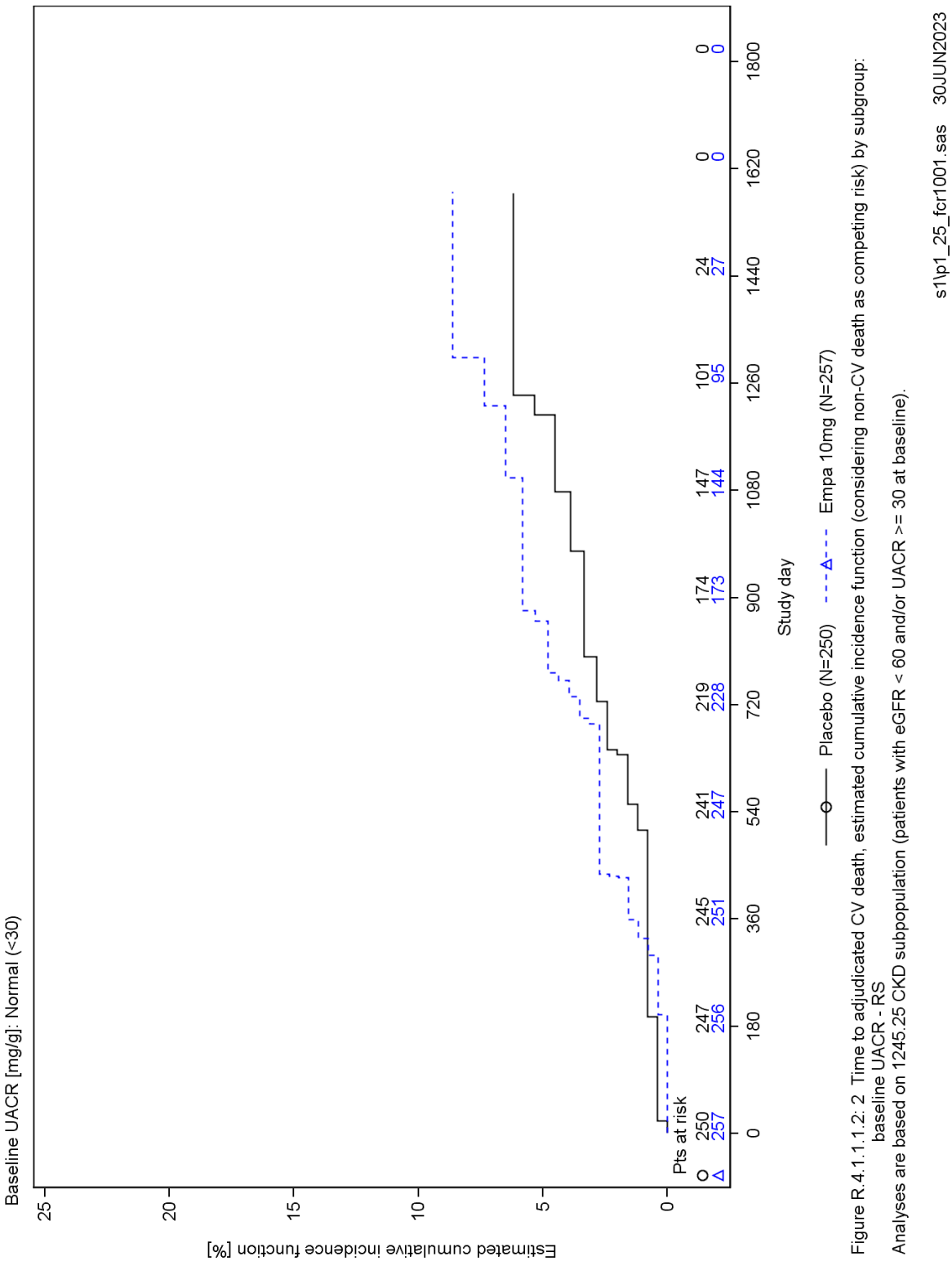


Figure R.4.1.1.1.2: 2 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) by subgroup: baseline UACR - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.1.2: 2**

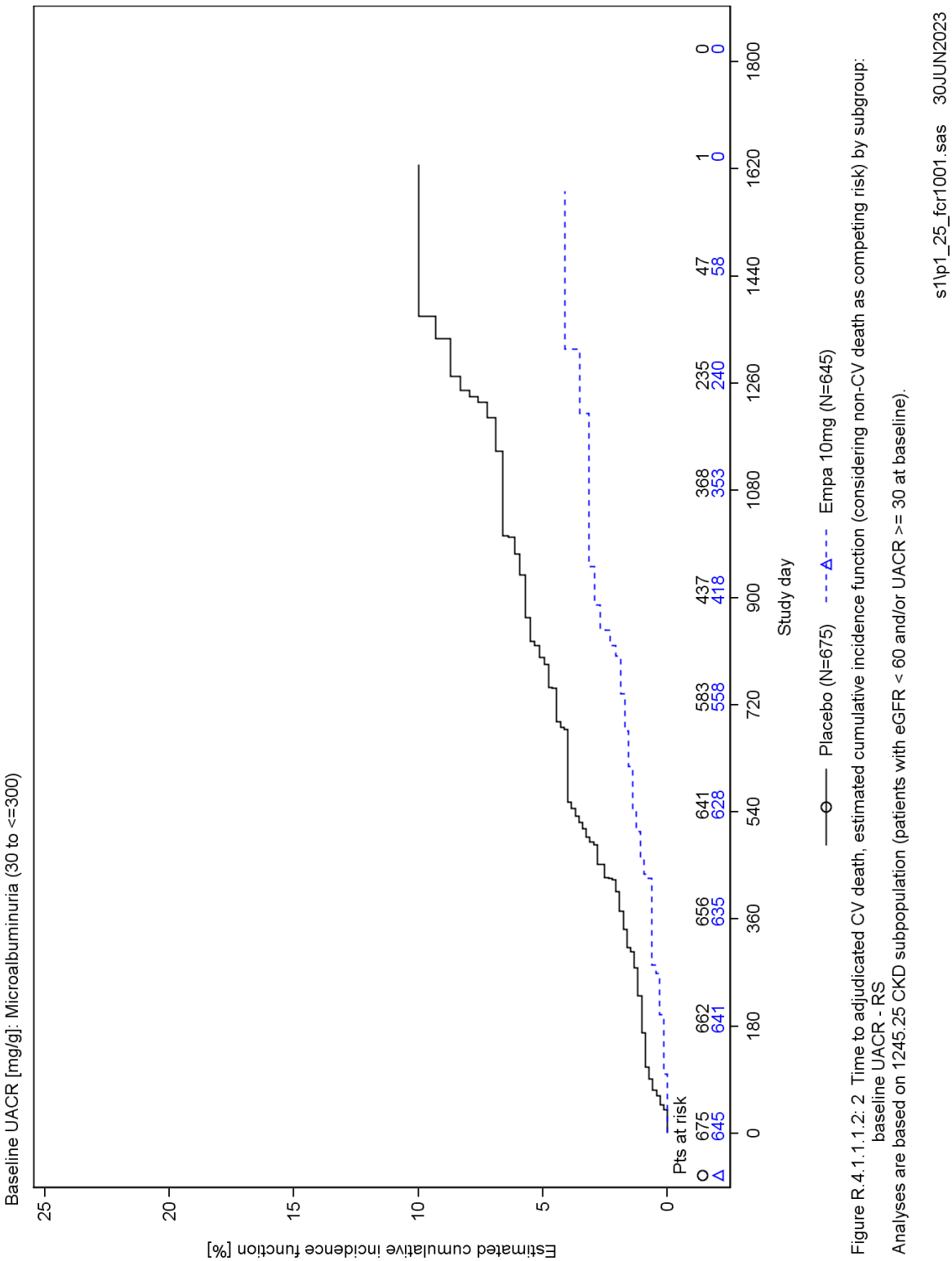


Figure R.4.1.1.1.2: 2 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) by subgroup: baseline UACR - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.1.2: 2**

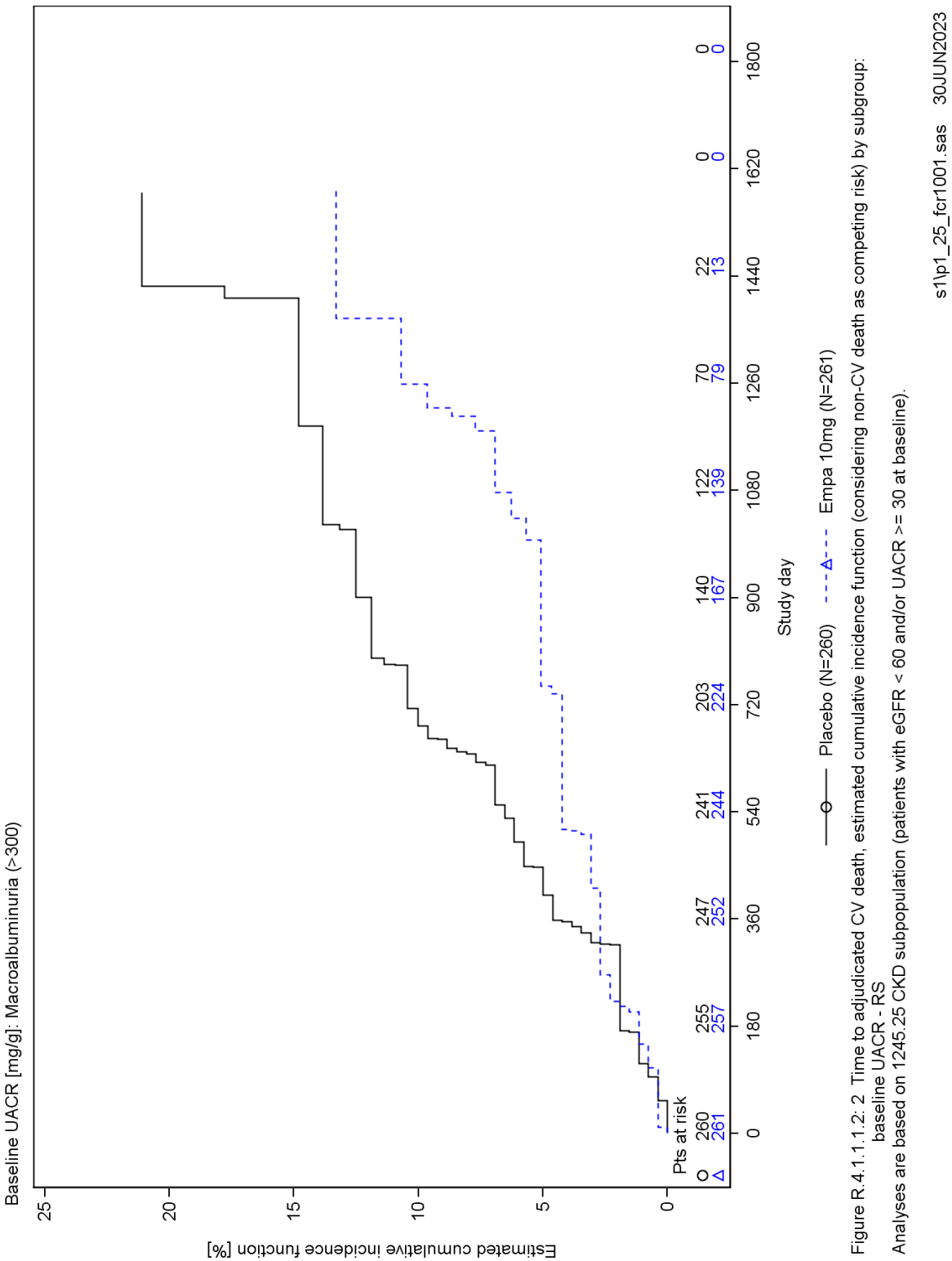


Figure R.4.1.1.1.2: 2 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) by subgroup: baseline UACR - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.4.1.1.1.3**

R.4.1.1.1.3 Time to renal death

Table R.4.1.1.1.3: 1 Cox Regression for time to renal death overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | Empa 10mg vs Placebo (95% CI) | Empa 10mg vs Placebo p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 0 | 0 | 0.00 | 1171 | 3 | 0.3 | 0.09 | >999.99 | | 0.9980 | |
| Sex | | | | | | | | | | | | |
| Male | 864 | 0 | 0 | 0.00 | 837 | 1 | 0.1 | 0.04 | | | | |
| Female | 324 | 0 | 0 | 0.00 | 334 | 2 | 0.6 | 0.20 | | | | |
| Age [years] | | | | | | | | | | | | |
| <65 | 569 | 0 | 0 | 0.00 | 547 | 1 | 0.2 | 0.06 | | | | |
| >=65 | 619 | 0 | 0 | 0.00 | 624 | 2 | 0.3 | 0.11 | | | | |
| Region | | | | | | | | | | | | |
| Europe | 468 | 0 | 0 | 0.00 | 434 | 1 | 0.2 | 0.08 | | | | |
| North America | 259 | 0 | 0 | 0.00 | 241 | 0 | 0 | 0.00 | | | | |
| Latin America | 177 | 0 | 0 | 0.00 | 191 | 0 | 0 | 0.00 | | | | |
| Africa | 50 | 0 | 0 | 0.00 | 54 | 1 | 1.9 | 0.66 | | | | |
| Asia | 234 | 0 | 0 | 0.00 | 251 | 1 | 0.4 | 0.13 | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | |
| <30 | 554 | 0 | 0 | 0.00 | 566 | 3 | 0.5 | 0.18 | | | | |
| >=30 | 634 | 0 | 0 | 0.00 | 605 | 0 | 0 | 0.00 | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 0.00 | 382 | 0 | 0 | 0.00 | | | | |
| >=130 | 809 | 0 | 0 | 0.00 | 789 | 3 | 0.4 | 0.13 | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 500 | 0 | 0 | 0.00 | 500 | 1 | 0.2 | 0.07 | | | | |
| 75 to <85 | 427 | 0 | 0 | 0.00 | 417 | 1 | 0.2 | 0.08 | | | | |
| >=85 | 261 | 0 | 0 | 0.00 | 254 | 1 | 0.4 | 0.14 | | | | |
| History of heart failure | | | | | | | | | | | | |
| No | 1048 | 0 | 0 | 0.00 | 1031 | 3 | 0.3 | 0.10 | | | | |
| Yes | 140 | 0 | 0 | 0.00 | 140 | 0 | 0 | 0.00 | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 0.00 | 178 | 1 | 0.6 | 0.20 | | | | |
| >=45 | 1009 | 0 | 0 | 0.00 | 993 | 2 | 0.2 | 0.07 | | | | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region and treatment.
Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.4.1.1.1.3: 1 Cox Regression for time to renal death overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | Empa 10mg vs Placebo (95% CI) | Empa 10mg vs Placebo p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 250 | 0 | 0 | 0.00 | 257 | 0 | 0 | 0.00 | | | | |
| Microalbuminuria (30 to <=300) | 675 | 0 | 0 | 0.00 | 645 | 1 | 0.2 | 0.05 | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 0.00 | 261 | 2 | 0.8 | 0.27 | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | |
| Low, moderate or high | 1018 | 0 | 0 | 0.00 | 1001 | 0 | 0 | 0.00 | | | | |
| Very high | 167 | 0 | 0 | 0.00 | 162 | 3 | 1.9 | 0.67 | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | |
| No | 205 | 0 | 0 | 0.00 | 211 | 0 | 0 | 0.00 | | | | |
| Yes | 983 | 0 | 0 | 0.00 | 960 | 3 | 0.3 | 0.11 | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | | |
| No | 422 | 0 | 0 | 0.00 | 408 | 1 | 0.2 | 0.08 | | | | |
| Yes | 766 | 0 | 0 | 0.00 | 763 | 2 | 0.3 | 0.09 | | | | |
| Baseline use of diuretics | | | | | | | | | | | | |
| No | 629 | 0 | 0 | 0.00 | 589 | 1 | 0.2 | 0.06 | | | | |
| Yes | 559 | 0 | 0 | 0.00 | 582 | 2 | 0.3 | 0.12 | | | | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region and treatment.
Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.1.3: 1**

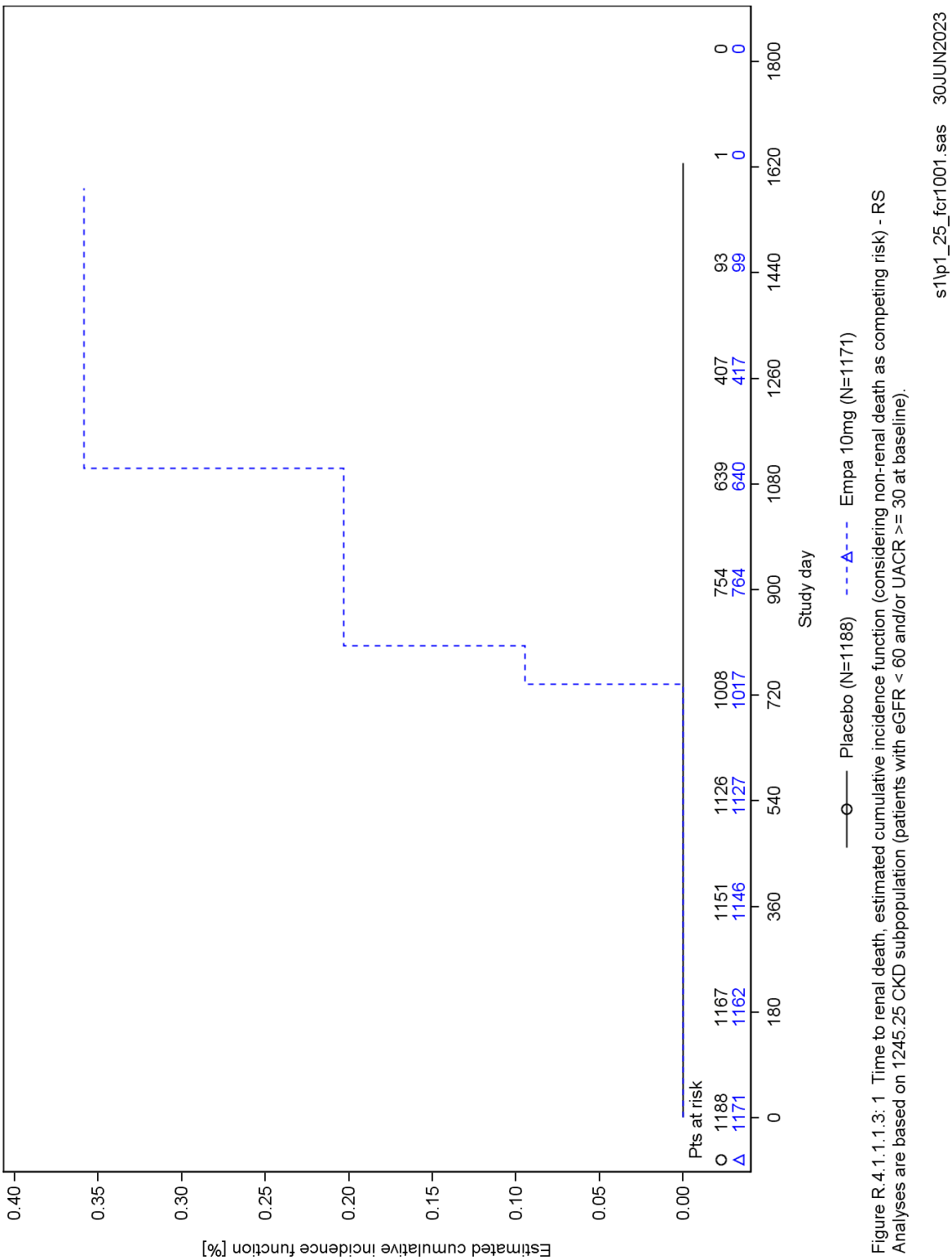


Figure R.4.1.1.1.3: 1 Time to renal death, estimated cumulative incidence function (considering non-renal death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.4.1.1.2**

R.4.1.1.2.1 Time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death

Table R.4.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1184 | 157 | 13.3 | 5.14 | 1161 | 96 | 8.3 | 3.07 | 0.58 | (0.45,0.75) | <0.0001 | |
| Sex | | | | | | | | | | | | 0.7159 |
| Male | 862 | 117 | 13.6 | 5.22 | 830 | 68 | 8.2 | 3.02 | 0.56 | (0.42,0.76) | 0.0002 | |
| Female | 322 | 40 | 12.4 | 4.94 | 331 | 28 | 8.5 | 3.20 | 0.62 | (0.38,1.01) | 0.0561 | |
| Age [years] | | | | | | | | | | | | 0.7396 |
| <65 | 566 | 74 | 13.1 | 4.92 | 542 | 47 | 8.7 | 3.08 | 0.61 | (0.42,0.87) | 0.0074 | |
| >=65 | 618 | 83 | 13.4 | 5.36 | 619 | 49 | 7.9 | 3.06 | 0.56 | (0.39,0.79) | 0.0012 | |
| Region | | | | | | | | | | | | 0.4007 |
| Europe | 466 | 51 | 10.9 | 4.13 | 431 | 37 | 8.6 | 3.19 | 0.76 | (0.50,1.17) | 0.2121 | |
| North America | 258 | 25 | 9.7 | 4.01 | 236 | 14 | 5.9 | 2.39 | 0.64 | (0.33,1.22) | 0.1750 | |
| Latin America | 177 | 34 | 19.2 | 7.89 | 189 | 21 | 11.1 | 4.16 | 0.49 | (0.29,0.85) | 0.0113 | |
| Africa | 50 | 9 | 18.0 | 7.07 | 54 | 7 | 13.0 | 4.99 | 0.66 | (0.24,1.76) | 0.4017 | |
| Asia | 233 | 38 | 16.3 | 5.99 | 251 | 17 | 6.8 | 2.32 | 0.39 | (0.22,0.68) | 0.0011 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5588 |
| <30 | 552 | 87 | 15.8 | 6.09 | 563 | 51 | 9.1 | 3.35 | 0.54 | (0.38,0.76) | 0.0005 | |
| >=30 | 632 | 70 | 11.1 | 4.31 | 598 | 45 | 7.5 | 2.80 | 0.63 | (0.43,0.91) | 0.0150 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.9239 |
| <130 | 377 | 44 | 11.7 | 4.53 | 379 | 26 | 6.9 | 2.54 | 0.57 | (0.35,0.92) | 0.0213 | |
| >=130 | 807 | 113 | 14.0 | 5.43 | 782 | 70 | 9.0 | 3.33 | 0.58 | (0.43,0.78) | 0.0004 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7010 |
| <75 | 497 | 58 | 11.7 | 4.47 | 496 | 36 | 7.3 | 2.70 | 0.58 | (0.38,0.89) | 0.0113 | |
| 75 to <85 | 427 | 61 | 14.3 | 5.66 | 413 | 33 | 8.0 | 2.95 | 0.51 | (0.34,0.78) | 0.0021 | |
| >=85 | 260 | 38 | 14.6 | 5.60 | 252 | 27 | 10.7 | 4.00 | 0.68 | (0.41,1.11) | 0.1254 | |
| History of heart failure | | | | | | | | | | | | 0.3714 |
| No | 1044 | 128 | 12.3 | 4.71 | 1022 | 76 | 7.4 | 2.72 | 0.55 | (0.41,0.73) | <0.0001 | |
| Yes | 140 | 29 | 20.7 | 8.72 | 139 | 20 | 14.4 | 5.97 | 0.74 | (0.42,1.31) | 0.2982 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >= 40% in eGFR from baseline.

Table R.4.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.3452 |
| <45 | 179 | 27 | 15.1 | 5.93 | 174 | 19 | 10.9 | 4.46 | 0.76 | (0.42,1.37) | 0.3571 | |
| >=45 | 1005 | 130 | 12.9 | 5.01 | 987 | 77 | 7.8 | 2.85 | 0.55 | (0.42,0.73) | <0.0001 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0510 |
| Normal (<30) | 250 | 20 | 8.0 | 3.06 | 253 | 21 | 8.3 | 3.01 | 0.98 | (0.53,1.81) | 0.9426 | |
| Microalbuminuria (30 to <=300) | 671 | 69 | 10.3 | 3.84 | 641 | 27 | 4.2 | 1.54 | 0.39 | (0.25,0.61) | <0.0001 | |
| Macroalbuminuria (>300) | 260 | 68 | 26.2 | 11.43 | 259 | 48 | 18.5 | 7.31 | 0.63 | (0.43,0.91) | 0.0133 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4876 |
| Low, moderate or high | 1014 | 113 | 11.1 | 4.25 | 994 | 67 | 6.7 | 2.45 | 0.56 | (0.41,0.76) | 0.0002 | |
| Very high | 167 | 44 | 26.3 | 11.25 | 159 | 29 | 18.2 | 7.75 | 0.68 | (0.43,1.09) | 0.1102 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9647 |
| No | 202 | 25 | 12.4 | 4.64 | 210 | 16 | 7.6 | 2.75 | 0.57 | (0.30,1.07) | 0.0804 | |
| Yes | 982 | 132 | 13.4 | 5.25 | 951 | 80 | 8.4 | 3.14 | 0.58 | (0.44,0.77) | 0.0001 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3086 |
| No | 420 | 67 | 16.0 | 6.36 | 405 | 36 | 8.9 | 3.33 | 0.49 | (0.33,0.74) | 0.0006 | |
| Yes | 764 | 90 | 11.8 | 4.50 | 756 | 60 | 7.9 | 2.94 | 0.64 | (0.46,0.89) | 0.0082 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.6289 |
| No | 625 | 57 | 9.1 | 3.50 | 585 | 37 | 6.3 | 2.32 | 0.62 | (0.41,0.94) | 0.0245 | |
| Yes | 559 | 100 | 17.9 | 7.03 | 576 | 59 | 10.2 | 3.86 | 0.55 | (0.39,0.75) | 0.0002 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >= 40% in eGFR from baseline.

**Figure R.4.1.1.2.1: 1**

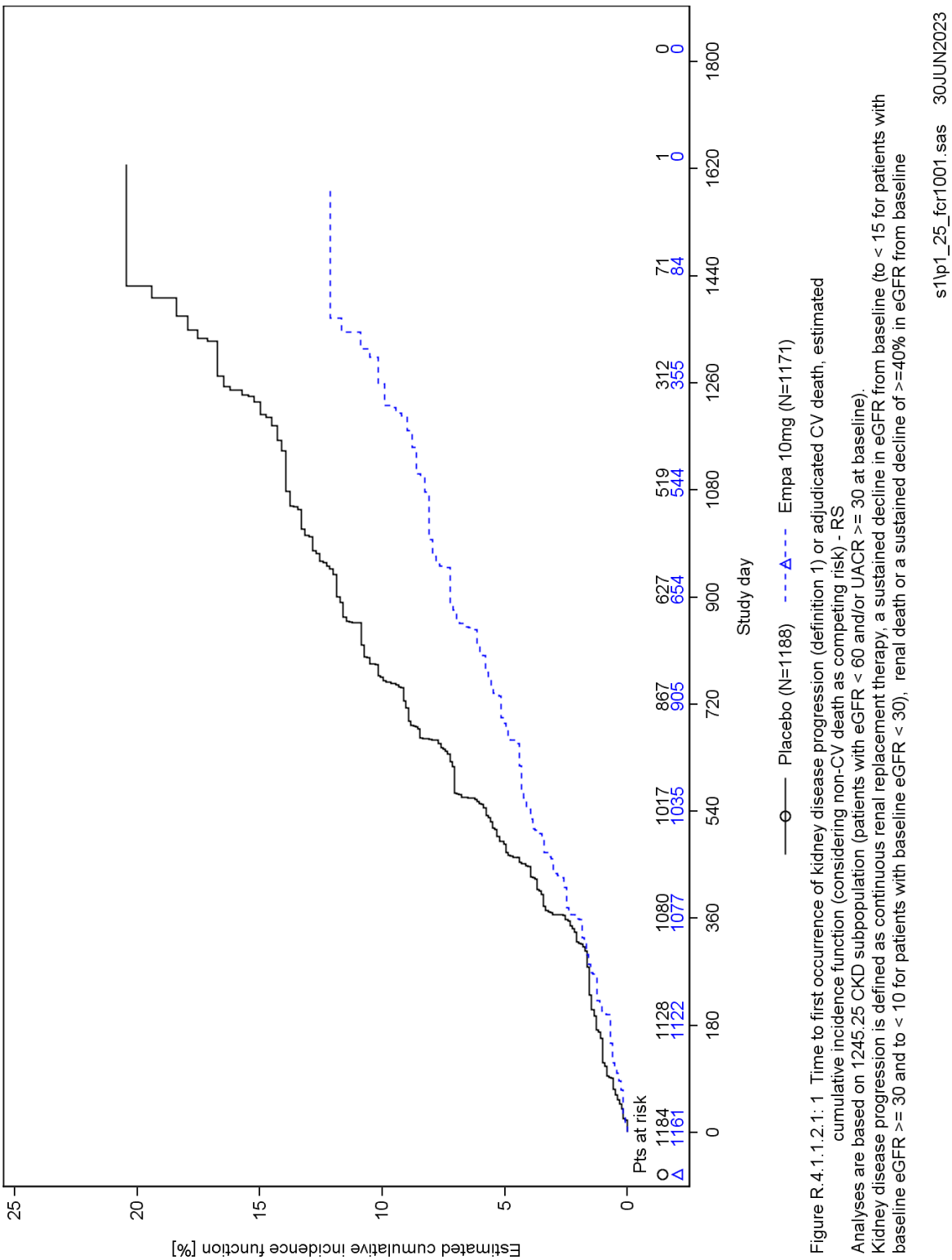


Figure R.4.1.1.2.1: 1 Time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >=40% in eGFR from baseline

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R.4.1.1.2.2 Time to first occurrence of kidney disease progression (definition 1)

Table R.4.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1183 | 66 | 5.6 | 2.19 | 1160 | 40 | 3.4 | 1.29 | 0.55 | (0.37,0.82) | 0.0034 | |
| Sex | | | | | | | | | | | | 0.2880 |
| Male | 862 | 44 | 5.1 | 1.98 | 829 | 30 | 3.6 | 1.34 | 0.64 | (0.40,1.02) | 0.0585 | |
| Female | 321 | 22 | 6.9 | 2.75 | 331 | 10 | 3.0 | 1.15 | 0.40 | (0.19,0.84) | 0.0152 | |
| Age [years] | | | | | | | | | | | | 0.7336 |
| <65 | 566 | 36 | 6.4 | 2.41 | 541 | 23 | 4.3 | 1.52 | 0.59 | (0.35,1.00) | 0.0487 | |
| >=65 | 617 | 30 | 4.9 | 1.96 | 619 | 17 | 2.7 | 1.07 | 0.51 | (0.28,0.93) | 0.0288 | |
| Region | | | | | | | | | | | | 0.9942 |
| Europe | 466 | 16 | 3.4 | 1.31 | 431 | 9 | 2.1 | 0.78 | 0.59 | (0.26,1.34) | 0.2104 | |
| North America | 258 | 11 | 4.3 | 1.78 | 236 | 5 | 2.1 | 0.86 | 0.54 | (0.19,1.57) | 0.2593 | |
| Latin America | 177 | 15 | 8.5 | 3.52 | 188 | 10 | 5.3 | 2.00 | 0.52 | (0.23,1.16) | 0.1101 | |
| Africa | 50 | 6 | 12.0 | 4.75 | 54 | 5 | 9.3 | 3.57 | 0.69 | (0.21,2.27) | 0.5440 | |
| Asia | 232 | 18 | 7.8 | 2.86 | 251 | 11 | 4.4 | 1.51 | 0.51 | (0.24,1.09) | 0.0824 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.4646 |
| <30 | 551 | 34 | 6.2 | 2.41 | 562 | 24 | 4.3 | 1.59 | 0.63 | (0.37,1.07) | 0.0860 | |
| >=30 | 632 | 32 | 5.1 | 1.99 | 598 | 16 | 2.7 | 1.01 | 0.47 | (0.26,0.86) | 0.0138 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.2864 |
| <130 | 376 | 13 | 3.5 | 1.35 | 379 | 11 | 2.9 | 1.08 | 0.81 | (0.36,1.81) | 0.6099 | |
| >=130 | 807 | 53 | 6.6 | 2.58 | 781 | 29 | 3.7 | 1.39 | 0.49 | (0.31,0.77) | 0.0021 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3378 |
| <75 | 496 | 22 | 4.4 | 1.71 | 496 | 10 | 2.0 | 0.76 | 0.40 | (0.19,0.85) | 0.0171 | |
| 75 to <85 | 427 | 25 | 5.9 | 2.35 | 412 | 20 | 4.9 | 1.80 | 0.78 | (0.43,1.41) | 0.4127 | |
| >=85 | 260 | 19 | 7.3 | 2.83 | 252 | 10 | 4.0 | 1.50 | 0.47 | (0.22,1.01) | 0.0532 | |
| History of heart failure | | | | | | | | | | | | 0.7380 |
| No | 1044 | 54 | 5.2 | 2.01 | 1021 | 33 | 3.2 | 1.19 | 0.55 | (0.35,0.84) | 0.0063 | |
| Yes | 139 | 12 | 8.6 | 3.66 | 139 | 7 | 5.0 | 2.12 | 0.65 | (0.25,1.66) | 0.3701 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >= 40% in eGFR from baseline.

Table R.4.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.5167 |
| <45 | 179 | 12 | 6.7 | 2.67 | 173 | 9 | 5.2 | 2.13 | 0.73 | (0.31,1.74) | 0.4783 | |
| >=45 | 1004 | 54 | 5.4 | 2.10 | 987 | 31 | 3.1 | 1.16 | 0.53 | (0.34,0.82) | 0.0047 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4529 |
| Normal (<30) | 249 | 9 | 3.6 | 1.38 | 253 | 4 | 1.6 | 0.58 | 0.42 | (0.13,1.35) | 0.1448 | |
| Microalbuminuria (30 to <=300) | 671 | 21 | 3.1 | 1.18 | 641 | 8 | 1.2 | 0.46 | 0.37 | (0.16,0.83) | 0.0162 | |
| Macroalbuminuria (>300) | 260 | 36 | 13.8 | 6.19 | 258 | 28 | 10.9 | 4.31 | 0.65 | (0.40,1.07) | 0.0905 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.8836 |
| Low, moderate or high | 1013 | 41 | 4.0 | 1.56 | 994 | 25 | 2.5 | 0.92 | 0.56 | (0.34,0.93) | 0.0242 | |
| Very high | 167 | 25 | 15.0 | 6.50 | 158 | 15 | 9.5 | 4.04 | 0.60 | (0.32,1.14) | 0.1178 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.8319 |
| No | 202 | 10 | 5.0 | 1.87 | 209 | 7 | 3.3 | 1.21 | 0.61 | (0.23,1.61) | 0.3185 | |
| Yes | 981 | 56 | 5.7 | 2.25 | 951 | 33 | 3.5 | 1.31 | 0.54 | (0.35,0.84) | 0.0058 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.2452 |
| No | 419 | 33 | 7.9 | 3.17 | 404 | 16 | 4.0 | 1.49 | 0.43 | (0.23,0.78) | 0.0053 | |
| Yes | 764 | 33 | 4.3 | 1.67 | 756 | 24 | 3.2 | 1.18 | 0.68 | (0.40,1.16) | 0.1560 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9670 |
| No | 625 | 24 | 3.8 | 1.48 | 584 | 14 | 2.4 | 0.88 | 0.54 | (0.28,1.05) | 0.0695 | |
| Yes | 558 | 42 | 7.5 | 3.00 | 576 | 26 | 4.5 | 1.71 | 0.55 | (0.34,0.90) | 0.0179 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >= 40% in eGFR from baseline.

**Figure R.4.1.1.2.2: 1**

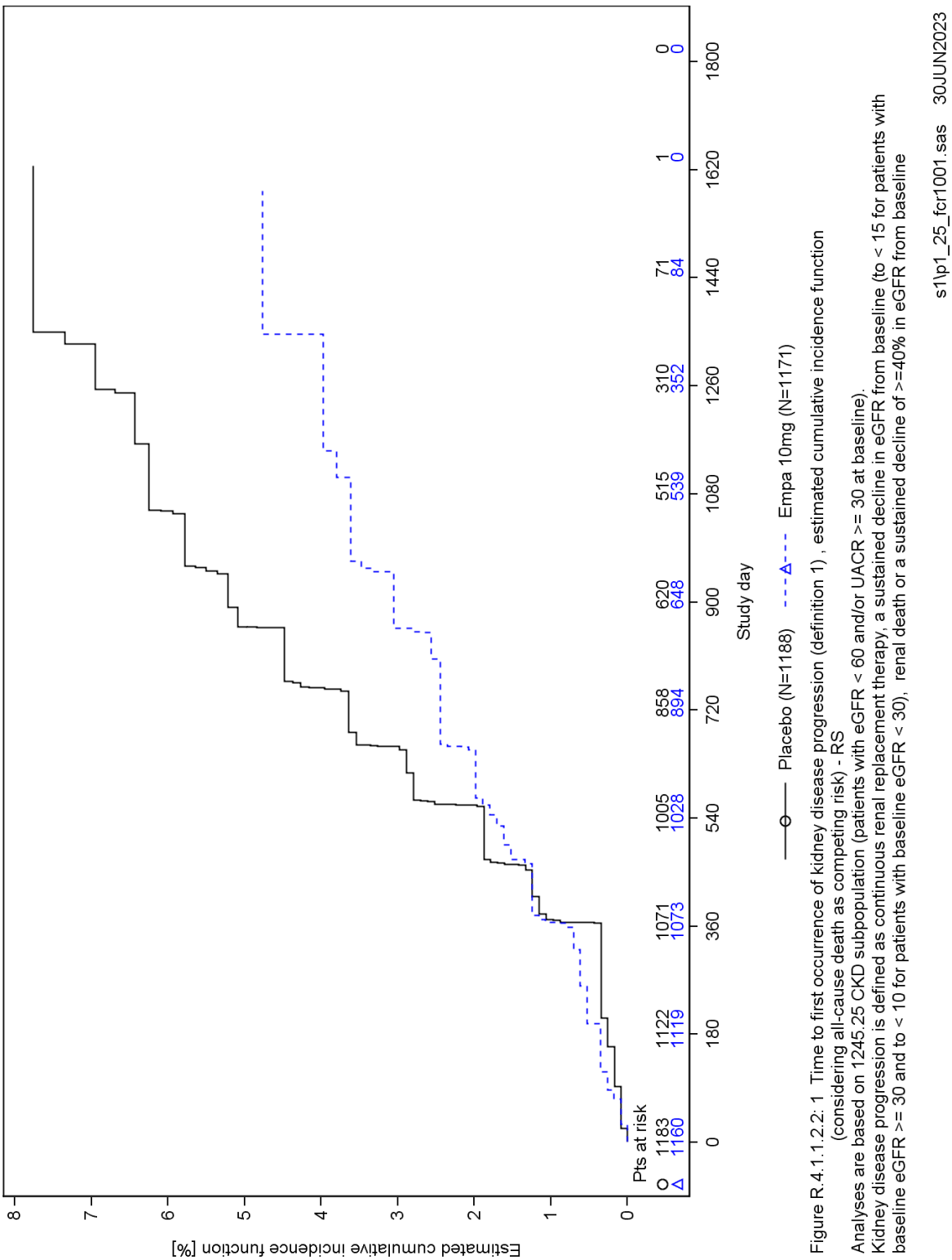


Figure R.4.1.1.2.2: 1 Time to first occurrence of kidney disease progression (definition 1) , estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >=40% in eGFR from baseline

R.4.1.1.2.3 Time to first occurrence of kidney disease progression (definition 2)

Table R.4.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1183 | 36 | 3.0 | 1.18 | 1160 | 21 | 1.8 | 0.67 | 0.54 | (0.31,0.92) | 0.0242 | |
| Sex | | | | | | | | | | | | 0.9629 |
| Male | 862 | 23 | 2.7 | 1.02 | 829 | 13 | 1.6 | 0.58 | 0.53 | (0.27,1.05) | 0.0699 | |
| Female | 321 | 13 | 4.0 | 1.60 | 331 | 8 | 2.4 | 0.92 | 0.55 | (0.23,1.32) | 0.1800 | |
| Age [years] | | | | | | | | | | | | 0.7695 |
| <65 | 566 | 24 | 4.2 | 1.59 | 541 | 13 | 2.4 | 0.85 | 0.50 | (0.26,0.99) | 0.0465 | |
| >=65 | 617 | 12 | 1.9 | 0.78 | 619 | 8 | 1.3 | 0.50 | 0.59 | (0.24,1.46) | 0.2561 | |
| Region | | | | | | | | | | | | 0.7262 |
| Europe | 466 | 7 | 1.5 | 0.57 | 431 | 4 | 0.9 | 0.35 | 0.57 | (0.17,1.96) | 0.3764 | |
| North America | 258 | 5 | 1.9 | 0.80 | 236 | 3 | 1.3 | 0.51 | 0.76 | (0.18,3.19) | 0.7063 | |
| Latin America | 177 | 11 | 6.2 | 2.53 | 188 | 5 | 2.7 | 0.98 | 0.36 | (0.13,1.05) | 0.0610 | |
| Africa | 50 | 2 | 4.0 | 1.53 | 54 | 3 | 5.6 | 2.12 | 1.47 | (0.24,8.85) | 0.6730 | |
| Asia | 232 | 11 | 4.7 | 1.72 | 251 | 6 | 2.4 | 0.82 | 0.46 | (0.17,1.26) | 0.1313 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.4563 |
| <30 | 551 | 22 | 4.0 | 1.54 | 562 | 15 | 2.7 | 0.98 | 0.62 | (0.32,1.20) | 0.1593 | |
| >=30 | 632 | 14 | 2.2 | 0.86 | 598 | 6 | 1.0 | 0.37 | 0.40 | (0.15,1.04) | 0.0613 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1493 |
| <130 | 376 | 5 | 1.3 | 0.51 | 379 | 6 | 1.6 | 0.58 | 1.17 | (0.36,3.86) | 0.7920 | |
| >=130 | 807 | 31 | 3.8 | 1.49 | 781 | 15 | 1.9 | 0.72 | 0.44 | (0.24,0.81) | 0.0088 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3632 |
| <75 | 496 | 10 | 2.0 | 0.77 | 496 | 4 | 0.8 | 0.30 | 0.34 | (0.11,1.10) | 0.0712 | |
| 75 to <85 | 427 | 13 | 3.0 | 1.21 | 412 | 11 | 2.7 | 0.98 | 0.85 | (0.38,1.92) | 0.7019 | |
| >=85 | 260 | 13 | 5.0 | 1.91 | 252 | 6 | 2.4 | 0.89 | 0.43 | (0.16,1.13) | 0.0854 | |
| History of heart failure | | | | | | | | | | | | 0.0826 |
| No | 1044 | 33 | 3.2 | 1.21 | 1021 | 17 | 1.7 | 0.61 | 0.45 | (0.25,0.81) | 0.0082 | |
| Yes | 139 | 3 | 2.2 | 0.89 | 139 | 4 | 2.9 | 1.19 | 1.91 | (0.42,8.64) | 0.4025 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >= 50% in eGFR from baseline.

Table R.4.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6570 |
| <45 | 179 | 9 | 5.0 | 1.98 | 173 | 6 | 3.5 | 1.41 | 0.67 | (0.24,1.91) | 0.4588 | |
| >=45 | 1004 | 27 | 2.7 | 1.04 | 987 | 15 | 1.5 | 0.56 | 0.51 | (0.27,0.96) | 0.0377 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.6054 |
| Normal (<30) | 249 | 4 | 1.6 | 0.61 | 253 | 2 | 0.8 | 0.29 | 0.47 | (0.09,2.57) | 0.3850 | |
| Microalbuminuria (30 to <=300) | 671 | 10 | 1.5 | 0.56 | 641 | 3 | 0.5 | 0.17 | 0.30 | (0.08,1.08) | 0.0652 | |
| Macroalbuminuria (>300) | 260 | 22 | 8.5 | 3.67 | 258 | 16 | 6.2 | 2.40 | 0.62 | (0.32,1.18) | 0.1440 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4691 |
| Low, moderate or high | 1013 | 22 | 2.2 | 0.83 | 994 | 11 | 1.1 | 0.40 | 0.47 | (0.23,0.97) | 0.0406 | |
| Very high | 167 | 14 | 8.4 | 3.52 | 158 | 10 | 6.3 | 2.66 | 0.70 | (0.31,1.59) | 0.3961 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9398 |
| No | 202 | 5 | 2.5 | 0.92 | 209 | 3 | 1.4 | 0.51 | 0.51 | (0.12,2.15) | 0.3611 | |
| Yes | 981 | 31 | 3.2 | 1.23 | 951 | 18 | 1.9 | 0.71 | 0.54 | (0.30,0.97) | 0.0408 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5954 |
| No | 419 | 19 | 4.5 | 1.80 | 404 | 10 | 2.5 | 0.92 | 0.46 | (0.21,0.99) | 0.0481 | |
| Yes | 764 | 17 | 2.2 | 0.85 | 756 | 11 | 1.5 | 0.54 | 0.62 | (0.29,1.32) | 0.2122 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.5383 |
| No | 625 | 16 | 2.6 | 0.98 | 584 | 8 | 1.4 | 0.50 | 0.44 | (0.19,1.03) | 0.0600 | |
| Yes | 558 | 20 | 3.6 | 1.40 | 576 | 13 | 2.3 | 0.85 | 0.63 | (0.31,1.26) | 0.1914 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >= 50% in eGFR from baseline.

**Figure R.4.1.1.2.3: 1**

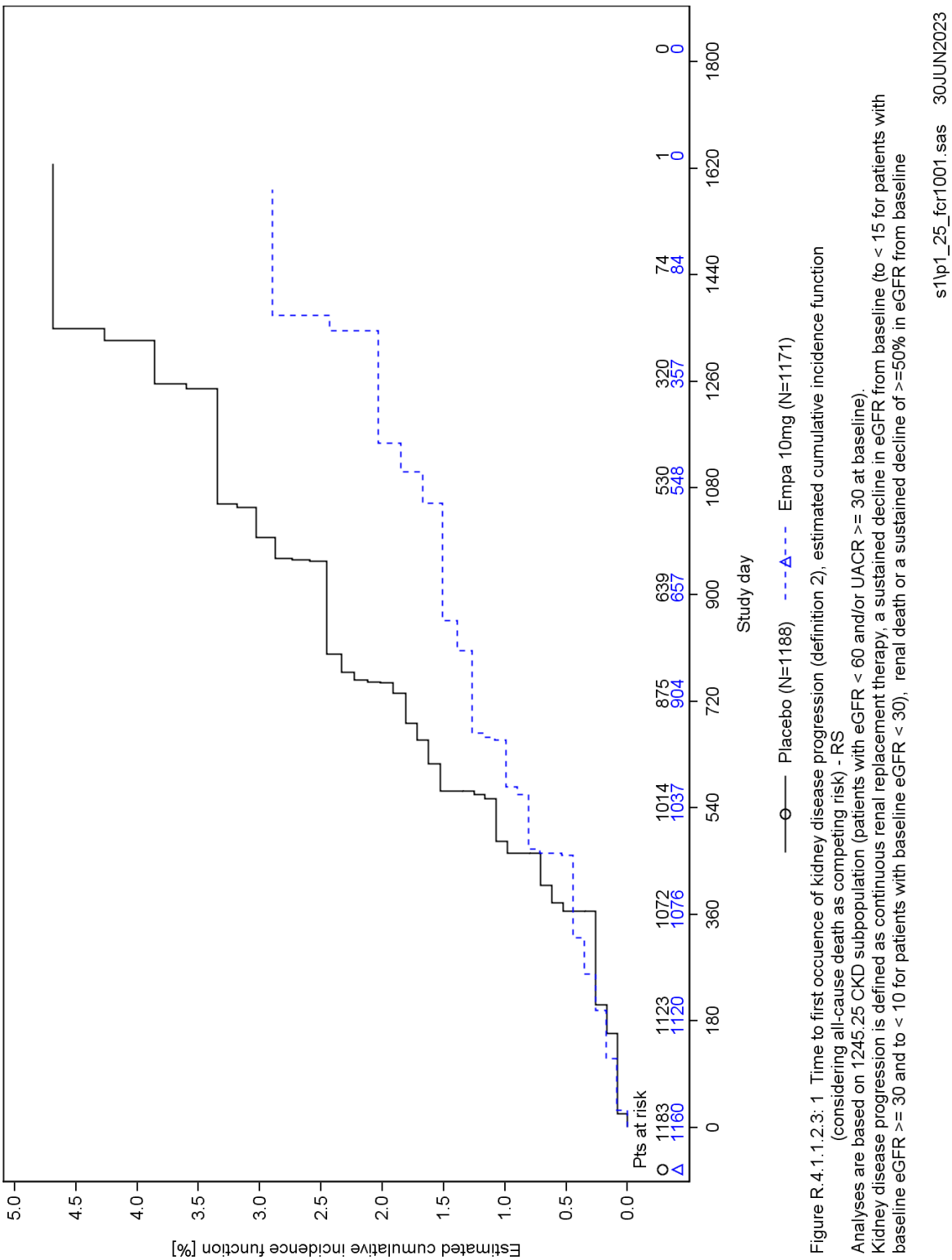


Figure R.4.1.1.2.3: 1 Time to first occuence of kidney disease progression (definition 2), estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >=50% in eGFR from baseline

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R.4.1.1.2.4 Time to first occurrence of kidney disease progression (definition 3)

Table R.4.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1183 | 30 | 2.5 | 0.98 | 1160 | 12 | 1.0 | 0.38 | 0.37 | (0.19,0.72) | 0.0035 | |
| Sex | | | | | | | | | | | | 0.3433 |
| Male | 862 | 20 | 2.3 | 0.89 | 829 | 6 | 0.7 | 0.27 | 0.28 | (0.11,0.70) | 0.0063 | |
| Female | 321 | 10 | 3.1 | 1.23 | 331 | 6 | 1.8 | 0.69 | 0.54 | (0.20,1.50) | 0.2365 | |
| Age [years] | | | | | | | | | | | | 0.6760 |
| <65 | 566 | 20 | 3.5 | 1.32 | 541 | 7 | 1.3 | 0.46 | 0.33 | (0.14,0.78) | 0.0115 | |
| >=65 | 617 | 10 | 1.6 | 0.65 | 619 | 5 | 0.8 | 0.31 | 0.44 | (0.15,1.29) | 0.1360 | |
| Region | | | | | | | | | | | | 0.7719 |
| Europe | 466 | 7 | 1.5 | 0.57 | 431 | 3 | 0.7 | 0.26 | 0.42 | (0.11,1.63) | 0.2112 | |
| North America | 258 | 3 | 1.2 | 0.48 | 236 | 1 | 0.4 | 0.17 | 0.43 | (0.04,4.19) | 0.4698 | |
| Latin America | 177 | 9 | 5.1 | 2.05 | 188 | 2 | 1.1 | 0.39 | 0.18 | (0.04,0.85) | 0.0299 | |
| Africa | 50 | 2 | 4.0 | 1.53 | 54 | 2 | 3.7 | 1.38 | 0.98 | (0.14,6.99) | 0.9827 | |
| Asia | 232 | 9 | 3.9 | 1.40 | 251 | 4 | 1.6 | 0.54 | 0.38 | (0.12,1.24) | 0.1088 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2386 |
| <30 | 551 | 19 | 3.4 | 1.32 | 562 | 10 | 1.8 | 0.65 | 0.48 | (0.22,1.03) | 0.0590 | |
| >=30 | 632 | 11 | 1.7 | 0.67 | 598 | 2 | 0.3 | 0.12 | 0.17 | (0.04,0.78) | 0.0224 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3248 |
| <130 | 376 | 4 | 1.1 | 0.41 | 379 | 3 | 0.8 | 0.29 | 0.73 | (0.16,3.27) | 0.6787 | |
| >=130 | 807 | 26 | 3.2 | 1.24 | 781 | 9 | 1.2 | 0.43 | 0.31 | (0.15,0.67) | 0.0027 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2862 |
| <75 | 496 | 8 | 1.6 | 0.61 | 496 | 2 | 0.4 | 0.15 | 0.21 | (0.05,1.01) | 0.0511 | |
| 75 to <85 | 427 | 10 | 2.3 | 0.93 | 412 | 7 | 1.7 | 0.62 | 0.69 | (0.26,1.83) | 0.4589 | |
| >=85 | 260 | 12 | 4.6 | 1.75 | 252 | 3 | 1.2 | 0.45 | 0.24 | (0.07,0.84) | 0.0260 | |
| History of heart failure | | | | | | | | | | | | 0.1715 |
| No | 1044 | 28 | 2.7 | 1.03 | 1021 | 10 | 1.0 | 0.36 | 0.31 | (0.15,0.65) | 0.0018 | |
| Yes | 139 | 2 | 1.4 | 0.59 | 139 | 2 | 1.4 | 0.59 | 1.37 | (0.19,9.83) | 0.7562 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >= 57% in eGFR from baseline.

Table R.4.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2717 |
| <45 | 179 | 8 | 4.5 | 1.74 | 173 | 5 | 2.9 | 1.17 | 0.64 | (0.21,1.99) | 0.4441 | |
| >=45 | 1004 | 22 | 2.2 | 0.84 | 987 | 7 | 0.7 | 0.26 | 0.29 | (0.12,0.68) | 0.0044 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8425 |
| Normal (<30) | 249 | 3 | 1.2 | 0.45 | 253 | 1 | 0.4 | 0.14 | 0.31 | (0.03,3.00) | 0.3130 | |
| Microalbuminuria (30 to <=300) | 671 | 8 | 1.2 | 0.44 | 641 | 2 | 0.3 | 0.11 | 0.25 | (0.05,1.17) | 0.0775 | |
| Macroalbuminuria (>300) | 260 | 19 | 7.3 | 3.14 | 258 | 9 | 3.5 | 1.34 | 0.41 | (0.18,0.91) | 0.0282 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.2601 |
| Low, moderate or high | 1013 | 18 | 1.8 | 0.68 | 994 | 5 | 0.5 | 0.18 | 0.26 | (0.10,0.70) | 0.0078 | |
| Very high | 167 | 12 | 7.2 | 2.99 | 158 | 7 | 4.4 | 1.85 | 0.57 | (0.22,1.46) | 0.2410 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9037 |
| No | 202 | 5 | 2.5 | 0.92 | 209 | 2 | 1.0 | 0.34 | 0.34 | (0.06,1.74) | 0.1934 | |
| Yes | 981 | 25 | 2.5 | 0.99 | 951 | 10 | 1.1 | 0.39 | 0.38 | (0.18,0.78) | 0.0091 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3285 |
| No | 419 | 17 | 4.1 | 1.60 | 404 | 5 | 1.2 | 0.46 | 0.26 | (0.10,0.70) | 0.0081 | |
| Yes | 764 | 13 | 1.7 | 0.65 | 756 | 7 | 0.9 | 0.34 | 0.51 | (0.20,1.28) | 0.1512 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.1593 |
| No | 625 | 14 | 2.2 | 0.86 | 584 | 3 | 0.5 | 0.19 | 0.19 | (0.05,0.65) | 0.0085 | |
| Yes | 558 | 16 | 2.9 | 1.12 | 576 | 9 | 1.6 | 0.58 | 0.55 | (0.24,1.25) | 0.1531 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >= 57% in eGFR from baseline.

**Figure R.4.1.1.2.4: 1**

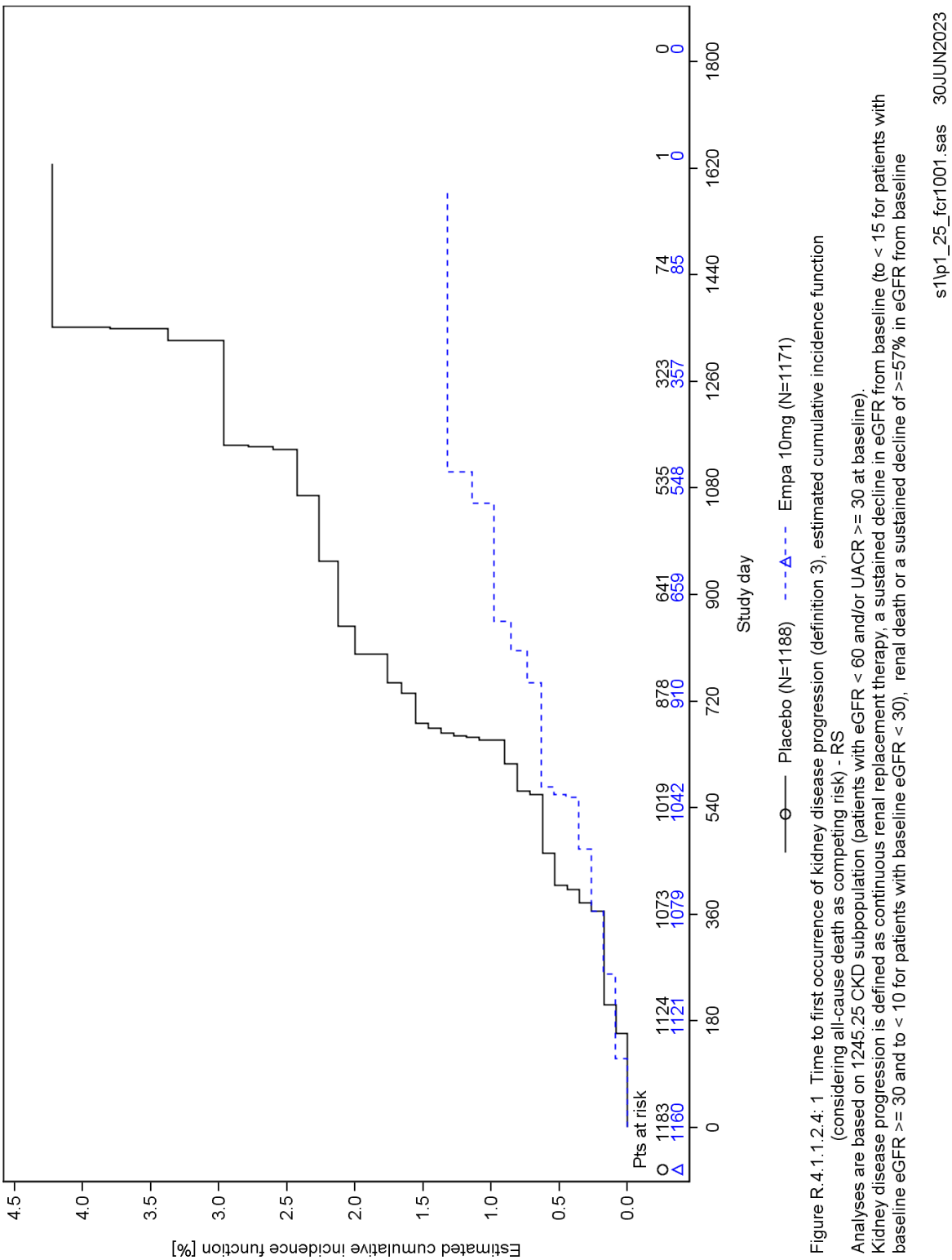


Figure R.4.1.1.2.4: 1 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as continuous renal replacement therapy, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), renal death or a sustained decline of >=57% in eGFR from baseline

R.4.1.1.2.5

R.4.1.1.2.5 Time to first occurrence of sustained decline of >= 40% in eGFR

Table R.4.1.1.2.5: 1 Cox Regression for time to first occurrence of sustained decline of >= 40% in eGFR overall - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1183 | 60 | 5.1 | 1.99 | 1160 | 36 | 3.1 | 1.16 | 0.55 | (0.37,0.84) | 0.0051 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region and treatment.
Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.2.5: 1**

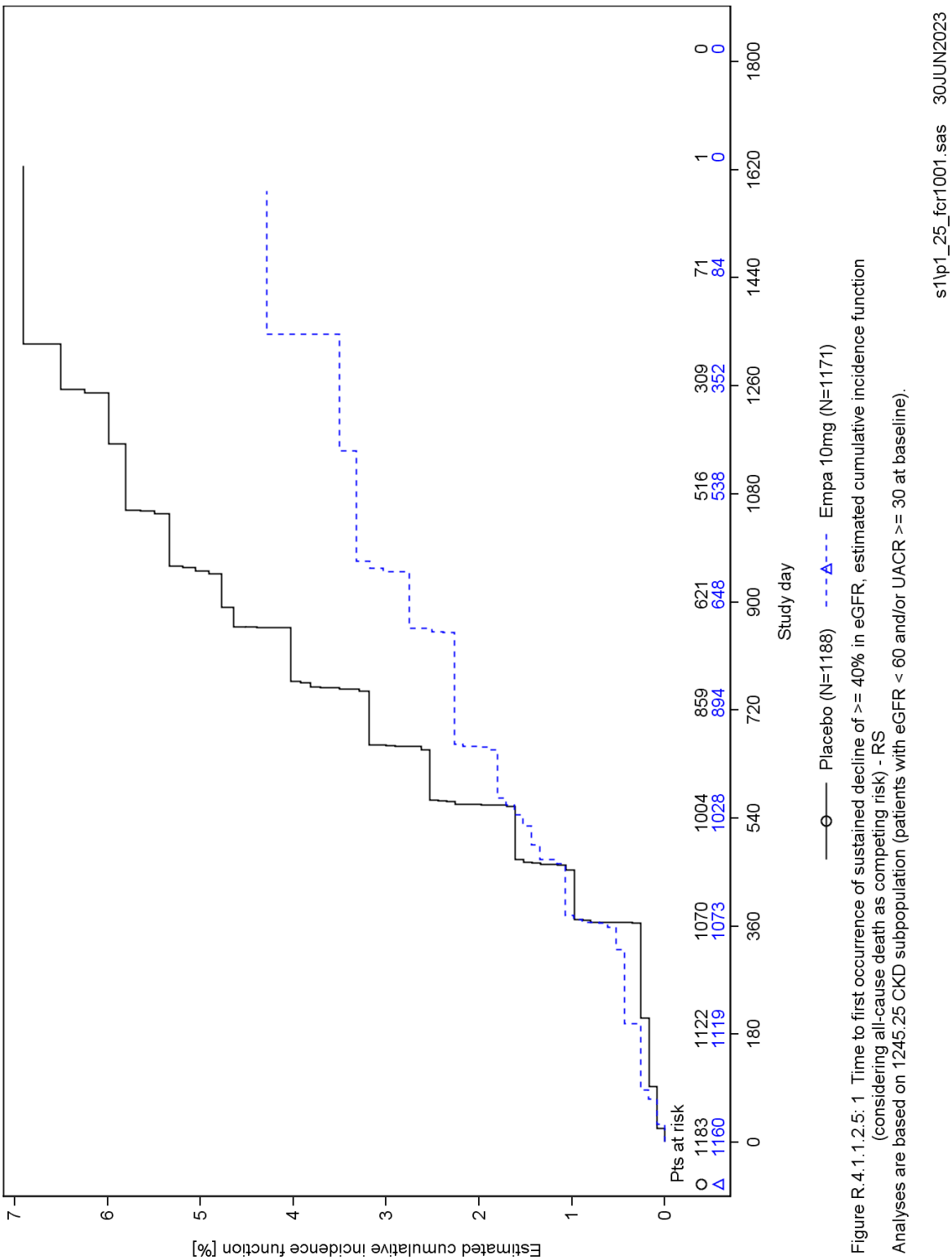


Figure R.4.1.1.2.5: 1 Time to first occurrence of sustained decline of >= 40% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.4.1.1.2.6 Time to first occurrence of sustained decline of >= 50% in eGFR

Table R.4.1.1.2.6: 1 Cox Regression for time to first occurrence of sustained decline of >= 50% in eGFR overall - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1183 | 28 | 2.4 | 0.92 | 1160 | 17 | 1.5 | 0.54 | 0.56 | (0.31,1.03) | 0.0615 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region and treatment.
Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.2.6: 1**

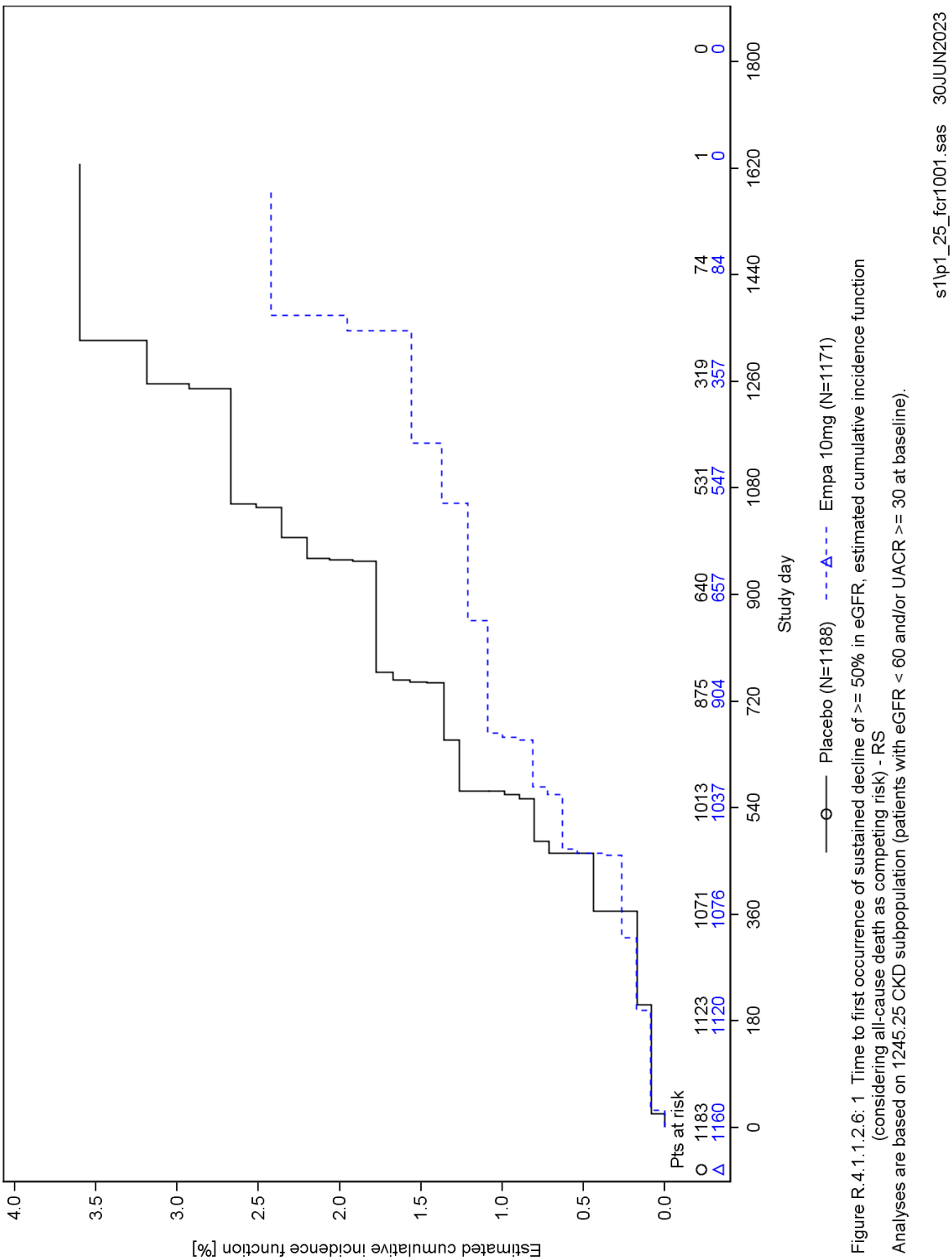


Figure R.4.1.1.2.6: 1 Time to first occurrence of sustained decline of >= 50% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.4.1.1.2.7

R.4.1.1.2.7 Time to first occurrence of sustained decline of >= 57% in eGFR

Table R.4.1.1.2.7: 1 Cox Regression for time to first occurrence of sustained decline of >= 57% in eGFR overall - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1183 | 22 | 1.9 | 0.72 | 1160 | 8 | 0.7 | 0.26 | 0.33 | (0.15,0.75) | 0.0081 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region and treatment.
Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.2.7: 1**

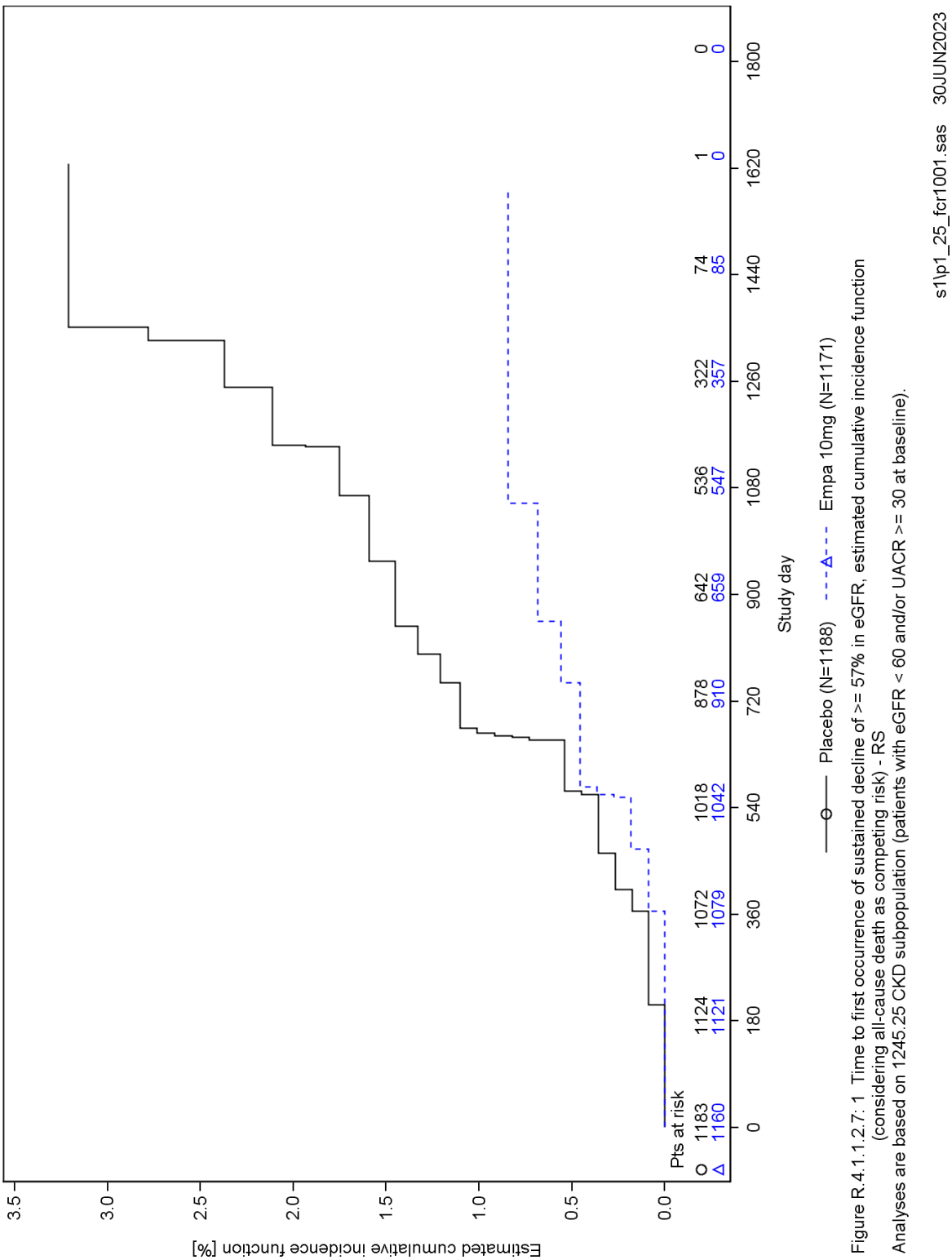


Figure R.4.1.1.2.7: 1 Time to first occurrence of sustained decline of >= 57% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.4.1.1.2.8**

R.4.1.1.2.8 Time to continuous renal replacement therapy

Table R.4.1.1.2.8: 1 Cox Regression for time to continuous renal replacement therapy overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 10 | 0.8 | 0.30 | 1171 | 2 | 0.2 | 0.06 | 0.18 | (0.04,0.81) | 0.0260 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region and treatment.
Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches.

**Figure R.4.1.1.2.8: 1**

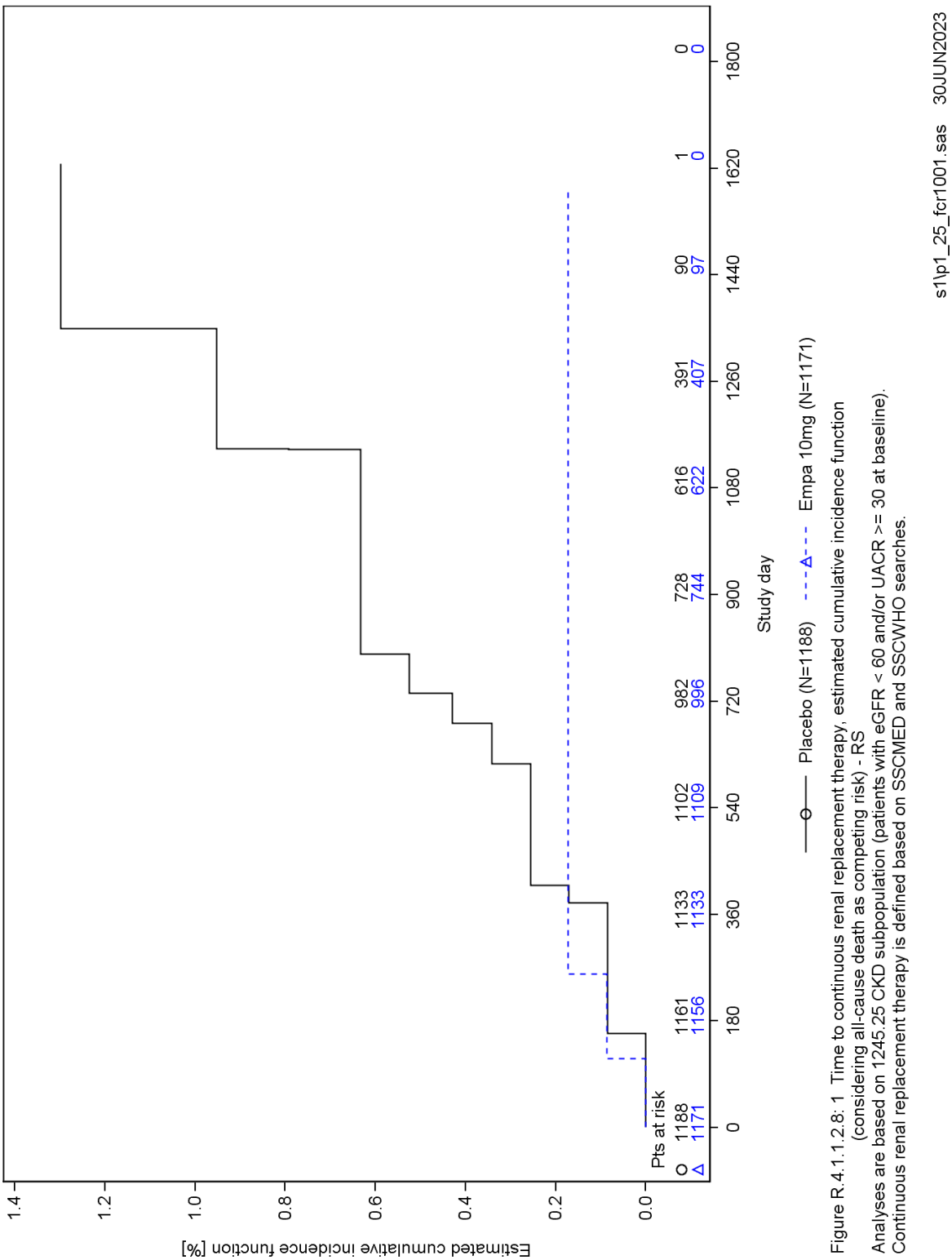


Figure R.4.1.1.2.8: 1 Time to continuous renal replacement therapy, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches.

R.4.1.1.2.9 Time to first occurrence of continuous renal replacement therapy, sustained decline in eGFR below defined threshold or renal death

Table R.4.1.1.2.9: 1 Cox Regression for time to first occurrence of continuous renal replacement therapy, sustained decline in eGFR below defined threshold or renal death overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1183 | 16 | 1.4 | 0.52 | 1160 | 8 | 0.7 | 0.25 | 0.44 | (0.19, 1.04) | 0.0623 | |
| Sex | | | | | | | | | | | | 0.7573 |
| Male | 862 | 10 | 1.2 | 0.44 | 829 | 4 | 0.5 | 0.18 | 0.39 | (0.12, 1.26) | 0.1161 | |
| Female | 321 | 6 | 1.9 | 0.73 | 331 | 4 | 1.2 | 0.46 | 0.52 | (0.14, 1.85) | 0.3095 | |
| Age [years] | | | | | | | | | | | | 0.2913 |
| <65 | 566 | 10 | 1.8 | 0.65 | 541 | 3 | 0.6 | 0.20 | 0.27 | (0.08, 1.00) | 0.0498 | |
| >=65 | 617 | 6 | 1.0 | 0.39 | 619 | 5 | 0.8 | 0.31 | 0.71 | (0.21, 2.33) | 0.5680 | |
| Region | | | | | | | | | | | | |
| Europe | 466 | 4 | 0.9 | 0.32 | 431 | 2 | 0.5 | 0.17 | | | | |
| North America | 258 | 0 | 0 | 0.00 | 236 | 1 | 0.4 | 0.17 | | | | |
| Latin America | 177 | 4 | 2.3 | 0.91 | 188 | 1 | 0.5 | 0.20 | | | | |
| Africa | 50 | 2 | 4.0 | 1.53 | 54 | 1 | 1.9 | 0.68 | | | | |
| Asia | 232 | 6 | 2.6 | 0.93 | 251 | 3 | 1.2 | 0.41 | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1790 |
| <30 | 551 | 9 | 1.6 | 0.62 | 562 | 7 | 1.2 | 0.46 | 0.67 | (0.25, 1.81) | 0.4279 | |
| >=30 | 632 | 7 | 1.1 | 0.43 | 598 | 1 | 0.2 | 0.06 | 0.14 | (0.02, 1.11) | 0.0626 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.6312 |
| <130 | 376 | 3 | 0.8 | 0.31 | 379 | 2 | 0.5 | 0.19 | 0.65 | (0.11, 3.90) | 0.6338 | |
| >=130 | 807 | 13 | 1.6 | 0.62 | 781 | 6 | 0.8 | 0.28 | 0.39 | (0.15, 1.04) | 0.0594 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 496 | 6 | 1.2 | 0.46 | 496 | 2 | 0.4 | 0.15 | | | | |
| 75 to <85 | 427 | 5 | 1.2 | 0.46 | 412 | 4 | 1.0 | 0.35 | | | | |
| >=85 | 260 | 5 | 1.9 | 0.72 | 252 | 2 | 0.8 | 0.30 | | | | |
| History of heart failure | | | | | | | | | | | | 0.4755 |
| No | 1044 | 15 | 1.4 | 0.55 | 1021 | 7 | 0.7 | 0.25 | 0.40 | (0.16, 0.99) | 0.0475 | |
| Yes | 139 | 1 | 0.7 | 0.29 | 139 | 1 | 0.7 | 0.30 | 1.17 | (0.07,18.95) | 0.9131 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

Table R.4.1.1.2.9: 1 Cox Regression for time to first occurrence of continuous renal replacement therapy, sustained decline in eGFR below defined threshold or renal death overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.5438 |
| <45 | 179 | 8 | 4.5 | 1.74 | 173 | 5 | 2.9 | 1.17 | 0.58 | (0.18, 1.84) | 0.3589 | |
| >=45 | 1004 | 8 | 0.8 | 0.31 | 987 | 3 | 0.3 | 0.11 | 0.34 | (0.09, 1.28) | 0.1097 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8683 |
| Normal (<30) | 249 | 3 | 1.2 | 0.45 | 253 | 1 | 0.4 | 0.14 | 0.30 | (0.03, 2.94) | 0.3042 | |
| Microalbuminuria (30 to <=300) | 671 | 3 | 0.4 | 0.17 | 641 | 2 | 0.3 | 0.11 | 0.64 | (0.11, 3.84) | 0.6245 | |
| Macroalbuminuria (>300) | 260 | 10 | 3.8 | 1.63 | 258 | 5 | 1.9 | 0.74 | 0.41 | (0.14, 1.21) | 0.1065 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3775 |
| Low, moderate or high | 1013 | 7 | 0.7 | 0.26 | 994 | 2 | 0.2 | 0.07 | 0.27 | (0.05, 1.28) | 0.0979 | |
| Very high | 167 | 9 | 5.4 | 2.22 | 158 | 6 | 3.8 | 1.58 | 0.62 | (0.22, 1.75) | 0.3676 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9438 |
| No | 202 | 4 | 2.0 | 0.73 | 209 | 2 | 1.0 | 0.34 | 0.47 | (0.09, 2.59) | 0.3872 | |
| Yes | 981 | 12 | 1.2 | 0.47 | 951 | 6 | 0.6 | 0.23 | 0.44 | (0.16, 1.18) | 0.1016 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5413 |
| No | 419 | 8 | 1.9 | 0.75 | 404 | 3 | 0.7 | 0.27 | 0.33 | (0.09, 1.24) | 0.1011 | |
| Yes | 764 | 8 | 1.0 | 0.40 | 756 | 5 | 0.7 | 0.24 | 0.56 | (0.18, 1.73) | 0.3157 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2827 |
| No | 625 | 7 | 1.1 | 0.43 | 584 | 2 | 0.3 | 0.13 | 0.23 | (0.05, 1.12) | 0.0692 | |
| Yes | 558 | 9 | 1.6 | 0.63 | 576 | 6 | 1.0 | 0.39 | 0.65 | (0.23, 1.86) | 0.4251 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.4.1.1.2.9: 1**

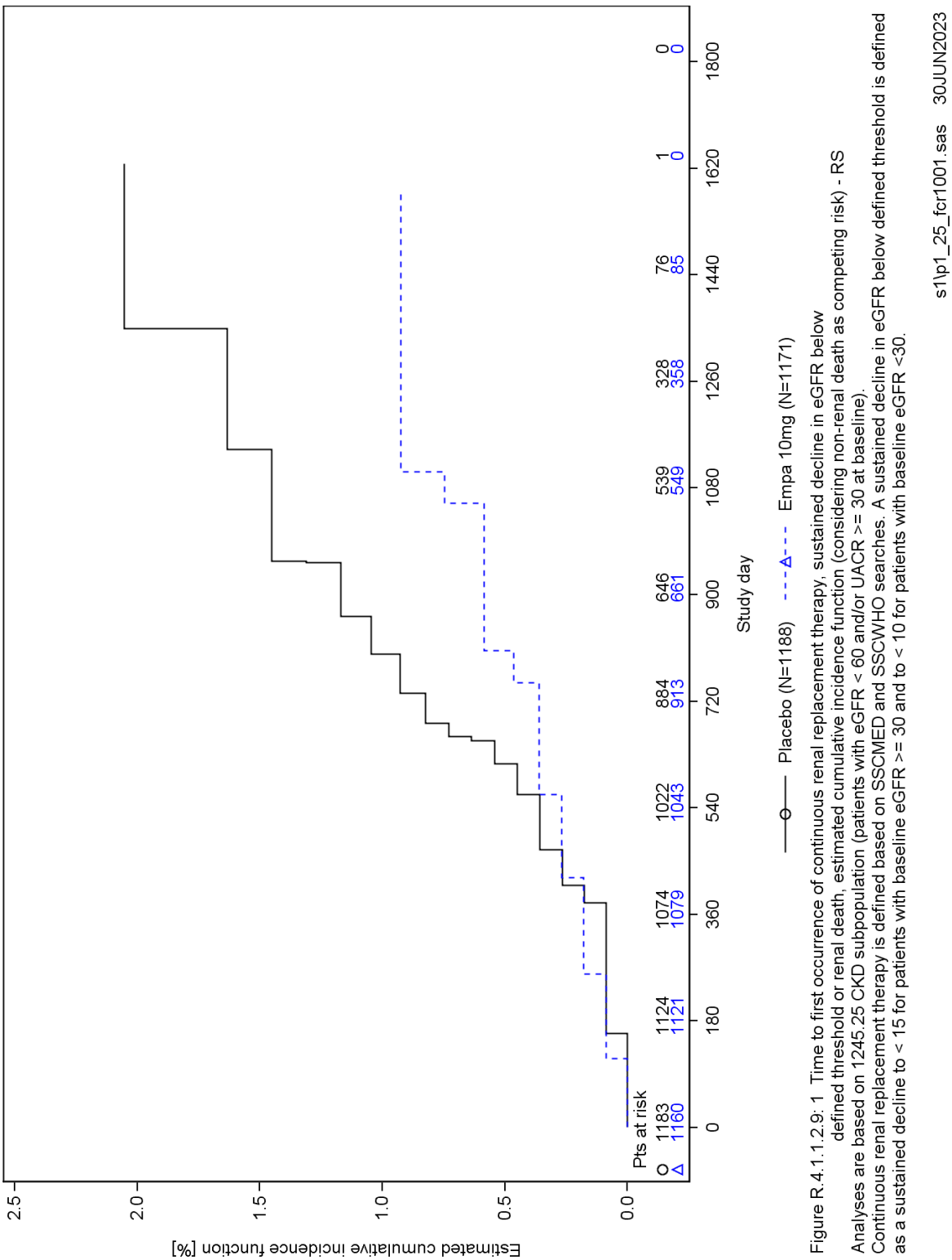


Figure R.4.1.1.2.9: 1 Time to first occurrence of continuous renal replacement therapy, sustained decline in eGFR below defined threshold or renal death, estimated cumulative incidence function (considering non-renal death as competing risk) - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

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R.4.1.1.2.10 Time to first occurrence of continuous renal replacement therapy or a sustained decline in eGFR below defined threshold

Table R.4.1.1.2.10: 1 Cox Regression for time to first occurrence of continuous renal replacement therapy or a sustained decline in eGFR below defined threshold overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1183 | 16 | 1.4 | 0.52 | 1160 | 6 | 0.5 | 0.19 | 0.33 | (0.13, 0.86) | 0.0223 | |
| Sex | | | | | | | | | | | | 0.7663 |
| Male | 862 | 10 | 1.2 | 0.44 | 829 | 3 | 0.4 | 0.13 | 0.29 | (0.08, 1.07) | 0.0630 | |
| Female | 321 | 6 | 1.9 | 0.73 | 331 | 3 | 0.9 | 0.34 | 0.39 | (0.10, 1.58) | 0.1868 | |
| Age [years] | | | | | | | | | | | | 0.6587 |
| <65 | 566 | 10 | 1.8 | 0.65 | 541 | 3 | 0.6 | 0.20 | 0.28 | (0.08, 1.00) | 0.0504 | |
| >=65 | 617 | 6 | 1.0 | 0.39 | 619 | 3 | 0.5 | 0.19 | 0.42 | (0.10, 1.70) | 0.2243 | |
| Region | | | | | | | | | | | | |
| Europe | 466 | 4 | 0.9 | 0.32 | 431 | 1 | 0.2 | 0.09 | | | | |
| North America | 258 | 0 | 0 | 0.00 | 236 | 1 | 0.4 | 0.17 | | | | |
| Latin America | 177 | 4 | 2.3 | 0.91 | 188 | 1 | 0.5 | 0.20 | | | | |
| Africa | 50 | 2 | 4.0 | 1.53 | 54 | 0 | 0 | 0.00 | | | | |
| Asia | 232 | 6 | 2.6 | 0.93 | 251 | 3 | 1.2 | 0.41 | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2920 |
| <30 | 551 | 9 | 1.6 | 0.62 | 562 | 5 | 0.9 | 0.33 | 0.48 | (0.16, 1.44) | 0.1905 | |
| >=30 | 632 | 7 | 1.1 | 0.43 | 598 | 1 | 0.2 | 0.06 | 0.13 | (0.02, 1.09) | 0.0607 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.4281 |
| <130 | 376 | 3 | 0.8 | 0.31 | 379 | 2 | 0.5 | 0.19 | 0.63 | (0.10, 3.78) | 0.6104 | |
| >=130 | 807 | 13 | 1.6 | 0.62 | 781 | 4 | 0.5 | 0.19 | 0.27 | (0.09, 0.82) | 0.0212 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 496 | 6 | 1.2 | 0.46 | 496 | 1 | 0.2 | 0.08 | | | | |
| 75 to <85 | 427 | 5 | 1.2 | 0.46 | 412 | 3 | 0.7 | 0.27 | | | | |
| >=85 | 260 | 5 | 1.9 | 0.72 | 252 | 2 | 0.8 | 0.30 | | | | |
| History of heart failure | | | | | | | | | | | | 0.3451 |
| No | 1044 | 15 | 1.4 | 0.55 | 1021 | 5 | 0.5 | 0.18 | 0.29 | (0.10, 0.79) | 0.0160 | |
| Yes | 139 | 1 | 0.7 | 0.29 | 139 | 1 | 0.7 | 0.30 | 1.20 | (0.07,19.46) | 0.8985 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

Table R.4.1.1.2.10: 1 Cox Regression for time to first occurrence of continuous renal replacement therapy or a sustained decline in eGFR below defined threshold overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4451 |
| <45 | 179 | 8 | 4.5 | 1.74 | 173 | 4 | 2.3 | 0.94 | 0.49 | (0.14, 1.66) | 0.2484 | |
| >=45 | 1004 | 8 | 0.8 | 0.31 | 987 | 2 | 0.2 | 0.07 | 0.22 | (0.05, 1.06) | 0.0586 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9949 |
| Normal (<30) | 249 | 3 | 1.2 | 0.45 | 253 | 1 | 0.4 | 0.14 | 0.30 | (0.03, 2.92) | 0.3022 | |
| Microalbuminuria (30 to <=300) | 671 | 3 | 0.4 | 0.17 | 641 | 1 | 0.2 | 0.06 | 0.31 | (0.03, 3.01) | 0.3143 | |
| Macroalbuminuria (>300) | 260 | 10 | 3.8 | 1.63 | 258 | 4 | 1.6 | 0.59 | 0.34 | (0.11, 1.09) | 0.0698 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.6349 |
| Low, moderate or high | 1013 | 7 | 0.7 | 0.26 | 994 | 2 | 0.2 | 0.07 | 0.26 | (0.05, 1.27) | 0.0956 | |
| Very high | 167 | 9 | 5.4 | 2.22 | 158 | 4 | 2.5 | 1.05 | 0.42 | (0.13, 1.38) | 0.1549 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6426 |
| No | 202 | 4 | 2.0 | 0.73 | 209 | 2 | 1.0 | 0.34 | 0.48 | (0.09, 2.62) | 0.3929 | |
| Yes | 981 | 12 | 1.2 | 0.47 | 951 | 4 | 0.4 | 0.16 | 0.29 | (0.09, 0.91) | 0.0340 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4846 |
| No | 419 | 8 | 1.9 | 0.75 | 404 | 2 | 0.5 | 0.18 | 0.22 | (0.05, 1.05) | 0.0578 | |
| Yes | 764 | 8 | 1.0 | 0.40 | 756 | 4 | 0.5 | 0.20 | 0.45 | (0.13, 1.49) | 0.1891 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2139 |
| No | 625 | 7 | 1.1 | 0.43 | 584 | 1 | 0.2 | 0.06 | 0.12 | (0.01, 0.97) | 0.0465 | |
| Yes | 558 | 9 | 1.6 | 0.63 | 576 | 5 | 0.9 | 0.32 | 0.53 | (0.18, 1.61) | 0.2655 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.4.1.1.2.10: 1**

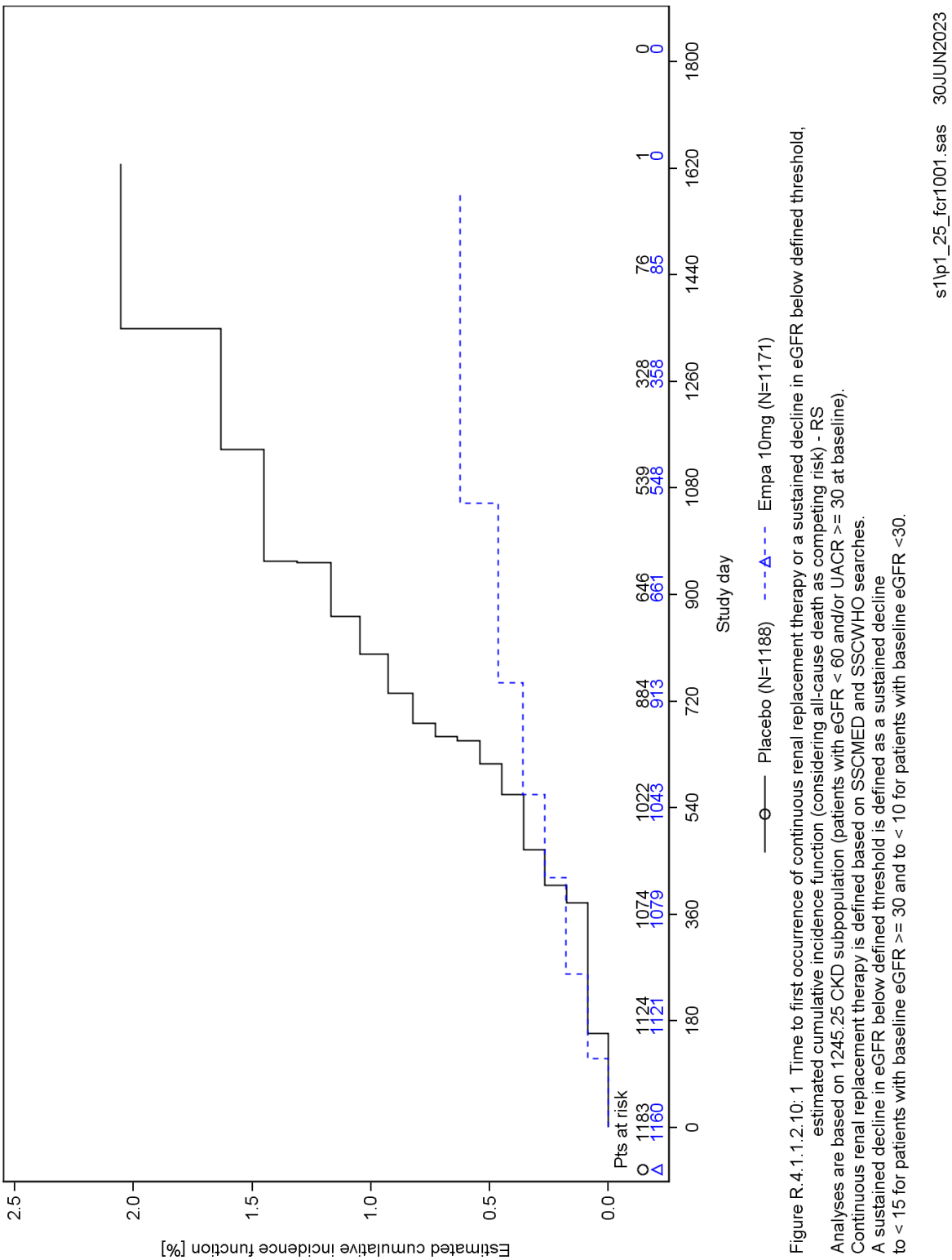


Figure R.4.1.1.2.10: 1 Time to first occurrence of continuous renal replacement therapy or a sustained decline in eGFR below defined threshold, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches.
A sustained decline in eGFR below defined threshold is defined as a sustained decline
to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

R.4.1.1.2.11 Time to first occurrence of sustained decline in eGFR below defined threshold

Table R.4.1.1.2.11: 1 Cox Regression for time to first occurrence of a sustained decline in eGFR below defined threshold overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1183 | 8 | 0.7 | 0.26 | 1160 | 4 | 0.3 | 0.13 | 0.44 | (0.13,1.48) | 0.1865 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region and treatment. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.4.1.1.2.11: 1**

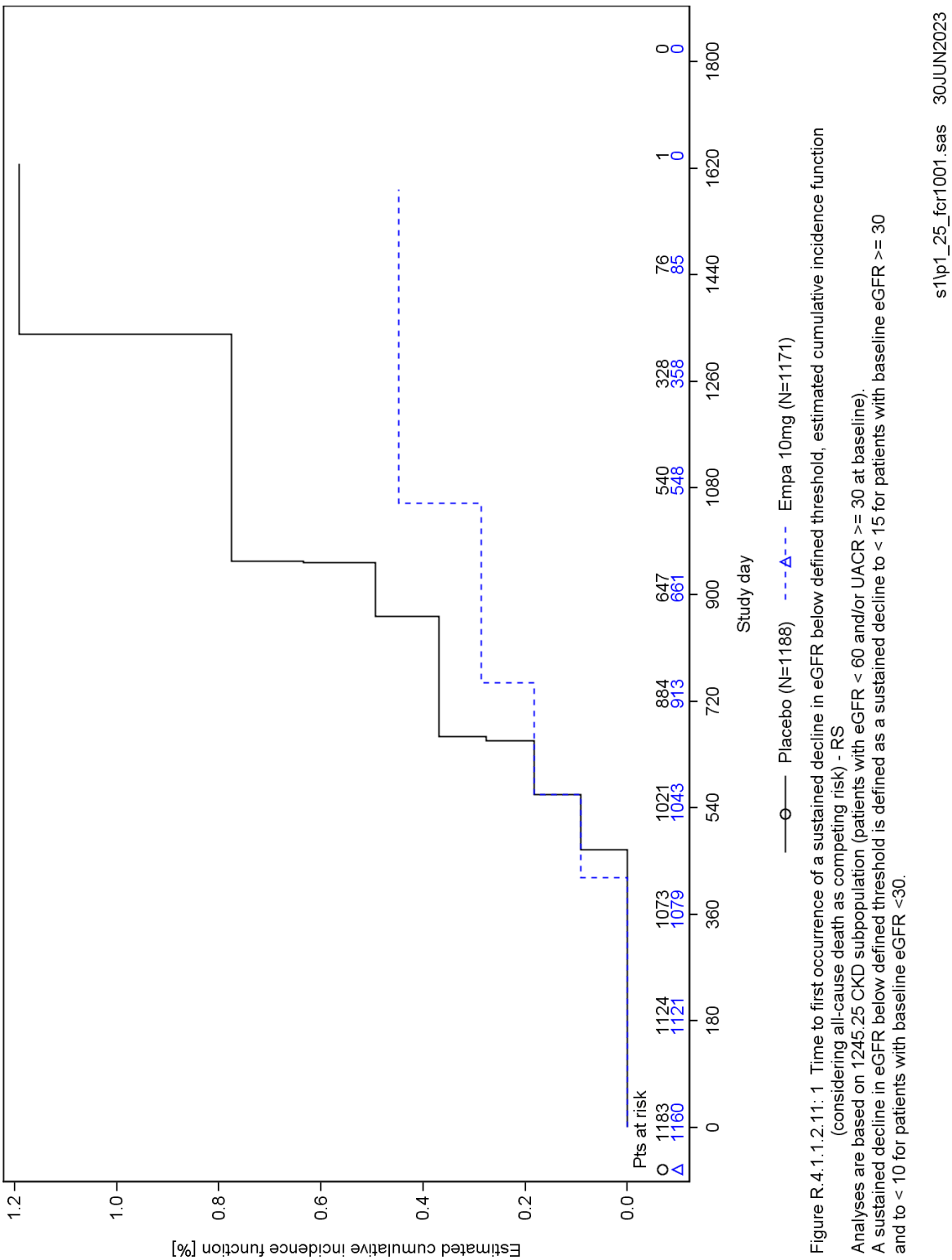


Figure R.4.1.1.2.11: 1 Time to first occurrence of a sustained decline in eGFR below defined threshold, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

R.4.1.1.2.12 Time to first occurrence of continuous renal replacement therapy or sustained decline in eGFR to <15mL/min/1.73m2

Table R.4.1.1.2.12: 1 Cox Regression for time to first occurrence of continuous renal replacement therapy or sustained decline in eGFR to <15mL/min/1.73m2 overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1183 | 16 | 1.4 | 0.52 | 1160 | 6 | 0.5 | 0.19 | 0.33 | (0.13, 0.86) | 0.0227 | |
| Sex | | | | | | | | | | | | 0.7586 |
| Male | 862 | 10 | 1.2 | 0.44 | 829 | 3 | 0.4 | 0.13 | 0.29 | (0.08, 1.07) | 0.0627 | |
| Female | 321 | 6 | 1.9 | 0.73 | 331 | 3 | 0.9 | 0.34 | 0.39 | (0.10, 1.59) | 0.1906 | |
| Age [years] | | | | | | | | | | | | 0.6638 |
| <65 | 566 | 10 | 1.8 | 0.65 | 541 | 3 | 0.6 | 0.20 | 0.28 | (0.08, 1.01) | 0.0515 | |
| >=65 | 617 | 6 | 1.0 | 0.39 | 619 | 3 | 0.5 | 0.19 | 0.42 | (0.10, 1.70) | 0.2240 | |
| Region | | | | | | | | | | | | |
| Europe | 466 | 4 | 0.9 | 0.32 | 431 | 1 | 0.2 | 0.09 | | | | |
| North America | 258 | 0 | 0 | 0.00 | 236 | 1 | 0.4 | 0.17 | | | | |
| Latin America | 177 | 4 | 2.3 | 0.91 | 188 | 1 | 0.5 | 0.20 | | | | |
| Africa | 50 | 2 | 4.0 | 1.53 | 54 | 0 | 0 | 0.00 | | | | |
| Asia | 232 | 6 | 2.6 | 0.93 | 251 | 3 | 1.2 | 0.41 | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2889 |
| <30 | 551 | 9 | 1.6 | 0.62 | 562 | 5 | 0.9 | 0.33 | 0.48 | (0.16, 1.45) | 0.1938 | |
| >=30 | 632 | 7 | 1.1 | 0.43 | 598 | 1 | 0.2 | 0.06 | 0.13 | (0.02, 1.09) | 0.0604 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.4241 |
| <130 | 376 | 3 | 0.8 | 0.31 | 379 | 2 | 0.5 | 0.19 | 0.63 | (0.10, 3.81) | 0.6163 | |
| >=130 | 807 | 13 | 1.6 | 0.62 | 781 | 4 | 0.5 | 0.19 | 0.27 | (0.09, 0.82) | 0.0212 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 496 | 6 | 1.2 | 0.46 | 496 | 1 | 0.2 | 0.08 | | | | |
| 75 to <85 | 427 | 5 | 1.2 | 0.46 | 412 | 3 | 0.7 | 0.27 | | | | |
| >=85 | 260 | 5 | 1.9 | 0.72 | 252 | 2 | 0.8 | 0.30 | | | | |
| History of heart failure | | | | | | | | | | | | 0.3421 |
| No | 1044 | 15 | 1.4 | 0.55 | 1021 | 5 | 0.5 | 0.18 | 0.29 | (0.10, 0.79) | 0.0162 | |
| Yes | 139 | 1 | 0.7 | 0.29 | 139 | 1 | 0.7 | 0.30 | 1.21 | (0.07,19.68) | 0.8923 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches.

Table R.4.1.1.2.12: 1 Cox Regression for time to first occurrence of continuous renal replacement therapy or sustained decline in eGFR to <15mL/min/1.73m2 overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4367 |
| <45 | 179 | 8 | 4.5 | 1.74 | 173 | 4 | 2.3 | 0.94 | 0.49 | (0.14, 1.68) | 0.2573 | |
| >=45 | 1004 | 8 | 0.8 | 0.31 | 987 | 2 | 0.2 | 0.07 | 0.22 | (0.05, 1.06) | 0.0586 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9932 |
| Normal (<30) | 249 | 3 | 1.2 | 0.45 | 253 | 1 | 0.4 | 0.14 | 0.30 | (0.03, 2.93) | 0.3023 | |
| Microalbuminuria (30 to <=300) | 671 | 3 | 0.4 | 0.17 | 641 | 1 | 0.2 | 0.06 | 0.31 | (0.03, 3.01) | 0.3138 | |
| Macroalbuminuria (>300) | 260 | 10 | 3.8 | 1.63 | 258 | 4 | 1.6 | 0.59 | 0.35 | (0.11, 1.11) | 0.0738 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.6225 |
| Low, moderate or high | 1013 | 7 | 0.7 | 0.26 | 994 | 2 | 0.2 | 0.07 | 0.26 | (0.05, 1.26) | 0.0955 | |
| Very high | 167 | 9 | 5.4 | 2.22 | 158 | 4 | 2.5 | 1.05 | 0.43 | (0.13, 1.41) | 0.1628 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6423 |
| No | 202 | 4 | 2.0 | 0.73 | 209 | 2 | 1.0 | 0.34 | 0.48 | (0.09, 2.62) | 0.3949 | |
| Yes | 981 | 12 | 1.2 | 0.47 | 951 | 4 | 0.4 | 0.16 | 0.29 | (0.09, 0.91) | 0.0344 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4875 |
| No | 419 | 8 | 1.9 | 0.75 | 404 | 2 | 0.5 | 0.18 | 0.22 | (0.05, 1.06) | 0.0587 | |
| Yes | 764 | 8 | 1.0 | 0.40 | 756 | 4 | 0.5 | 0.20 | 0.45 | (0.13, 1.49) | 0.1896 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2129 |
| No | 625 | 7 | 1.1 | 0.43 | 584 | 1 | 0.2 | 0.06 | 0.12 | (0.01, 0.97) | 0.0466 | |
| Yes | 558 | 9 | 1.6 | 0.63 | 576 | 5 | 0.9 | 0.32 | 0.54 | (0.18, 1.62) | 0.2695 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches.

**Figure R.4.1.1.2.12: 1**

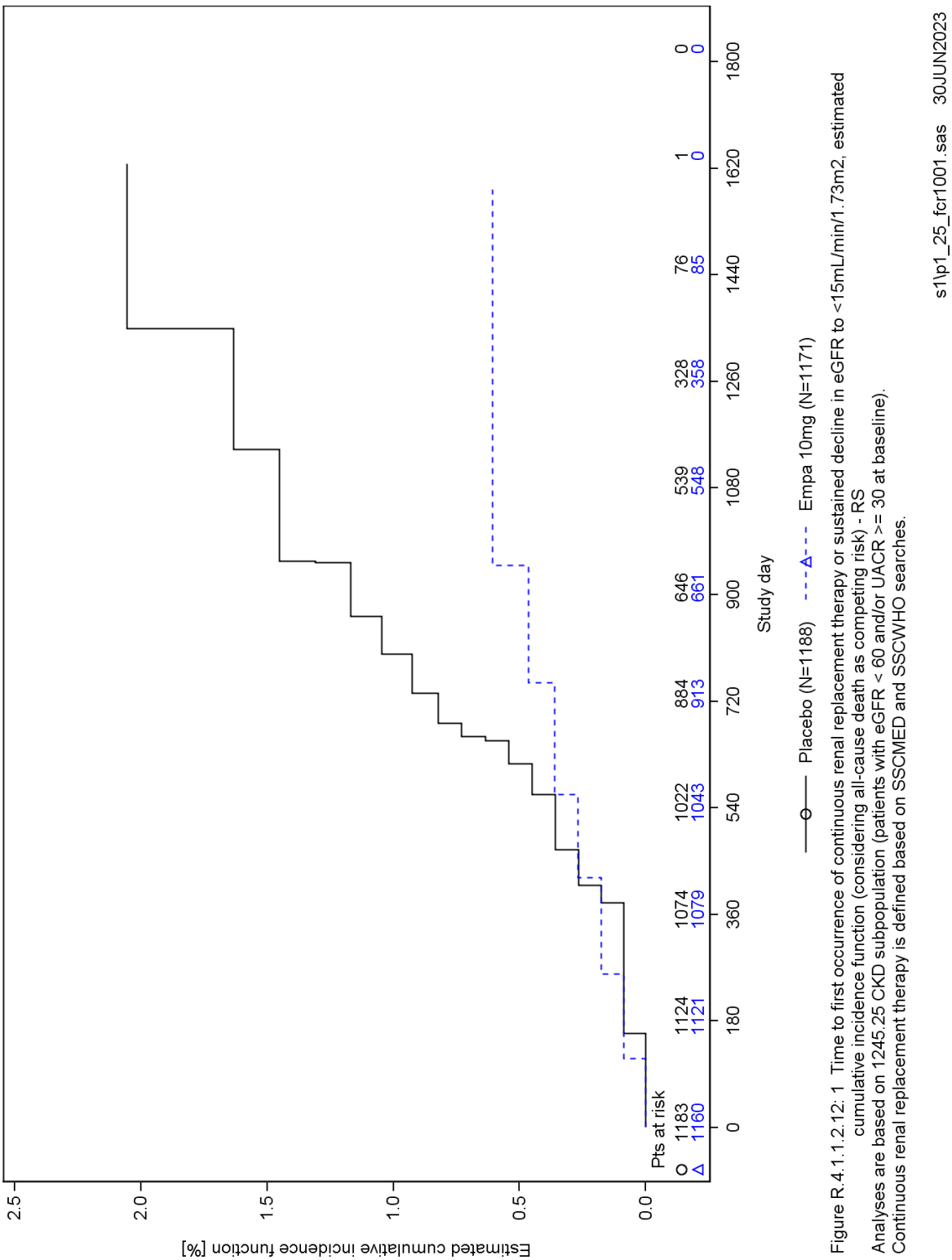


Figure R.4.1.1.2.12: 1 Time to first occurrence of continuous renal replacement therapy or sustained decline in eGFR to <15mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Continuous renal replacement therapy is defined based on SSCMED and SSCWHO searches.

R.4.1.1.2.13 Time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2

Table R.4.1.1.2.13: 1 Cox Regression for time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2
overall - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1183 | 8 | 0.7 | 0.26 | 1160 | 4 | 0.3 | 0.13 | 0.45 | (0.13,1.50) | 0.1933 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region and treatment.
Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.2.13: 1**

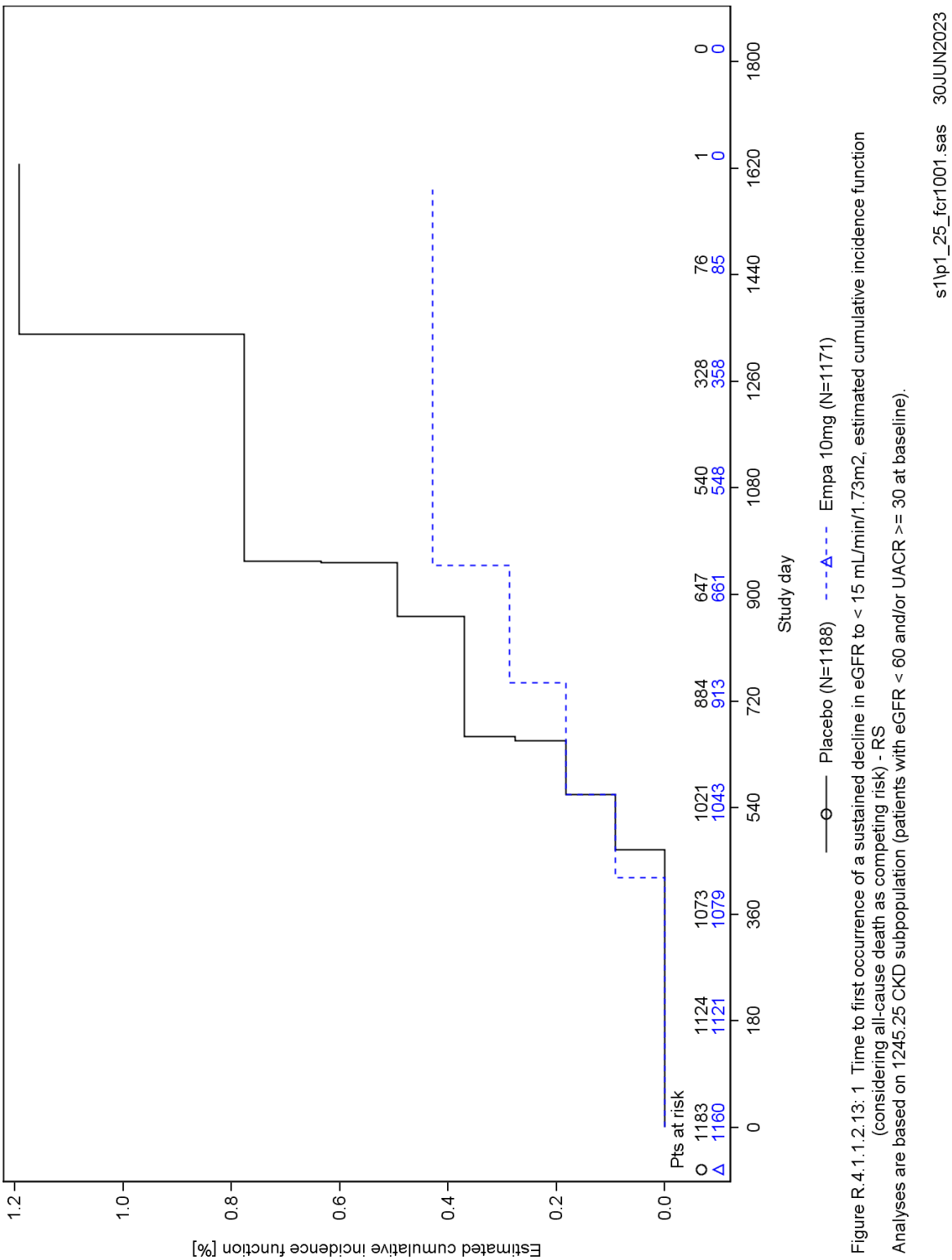


Figure R.4.1.1.2.13: 1 Time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.4.1.1.2.14 Time to first occurrence of acute kidney injury

Table R.4.1.1.2.14: 1 Cox Regression for time to first occurrence of acute kidney injury overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1188 | 37 | 3.1 | 1.12 | 1171 | 22 | 1.9 | 0.66 | 0.62 | (0.37, 1.06) | 0.0785 | |
| Sex | | | | | | | | | | | | 0.9240 |
| Male | 864 | 28 | 3.2 | 1.16 | 837 | 16 | 1.9 | 0.67 | 0.63 | (0.34, 1.17) | 0.1431 | |
| Female | 324 | 9 | 2.8 | 0.99 | 334 | 6 | 1.8 | 0.63 | 0.60 | (0.21, 1.68) | 0.3262 | |
| Age [years] | | | | | | | | | | | | 0.9353 |
| <65 | 569 | 12 | 2.1 | 0.75 | 547 | 7 | 1.3 | 0.43 | 0.60 | (0.24, 1.53) | 0.2861 | |
| >=65 | 619 | 25 | 4.0 | 1.46 | 624 | 15 | 2.4 | 0.87 | 0.63 | (0.33, 1.20) | 0.1582 | |
| Region | | | | | | | | | | | | 0.5149 |
| Europe | 468 | 9 | 1.9 | 0.68 | 434 | 6 | 1.4 | 0.49 | 0.74 | (0.26, 2.08) | 0.5688 | |
| North America | 259 | 16 | 6.2 | 2.28 | 241 | 11 | 4.6 | 1.66 | 0.78 | (0.36, 1.68) | 0.5234 | |
| Latin America | 177 | 2 | 1.1 | 0.41 | 191 | 1 | 0.5 | 0.19 | 0.39 | (0.04, 4.33) | 0.4449 | |
| Africa | 50 | 1 | 2.0 | 0.70 | 54 | 2 | 3.7 | 1.32 | 1.69 | (0.15,18.71) | 0.6680 | |
| Asia | 234 | 9 | 3.8 | 1.35 | 251 | 2 | 0.8 | 0.26 | 0.20 | (0.04, 0.94) | 0.0416 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7296 |
| <30 | 554 | 16 | 2.9 | 1.03 | 566 | 9 | 1.6 | 0.55 | 0.56 | (0.25, 1.26) | 0.1619 | |
| >=30 | 634 | 21 | 3.3 | 1.19 | 605 | 13 | 2.1 | 0.76 | 0.67 | (0.34, 1.35) | 0.2634 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3121 |
| <130 | 379 | 17 | 4.5 | 1.62 | 382 | 7 | 1.8 | 0.64 | 0.44 | (0.18, 1.06) | 0.0669 | |
| >=130 | 809 | 20 | 2.5 | 0.88 | 789 | 15 | 1.9 | 0.67 | 0.78 | (0.40, 1.52) | 0.4612 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3883 |
| <75 | 500 | 16 | 3.2 | 1.13 | 500 | 9 | 1.8 | 0.62 | 0.58 | (0.26, 1.31) | 0.1908 | |
| 75 to <85 | 427 | 16 | 3.7 | 1.36 | 417 | 6 | 1.4 | 0.51 | 0.44 | (0.17, 1.12) | 0.0848 | |
| >=85 | 261 | 5 | 1.9 | 0.68 | 254 | 7 | 2.8 | 0.98 | 1.22 | (0.39, 3.87) | 0.7320 | |
| History of heart failure | | | | | | | | | | | | 0.5347 |
| No | 1048 | 29 | 2.8 | 0.98 | 1031 | 15 | 1.5 | 0.50 | 0.55 | (0.29, 1.02) | 0.0597 | |
| Yes | 140 | 8 | 5.7 | 2.23 | 140 | 7 | 5.0 | 1.96 | 0.80 | (0.29, 2.21) | 0.6683 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 18.0.

Table R.4.1.1.2.14: 1 Cox Regression for time to first occurrence of acute kidney injury overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6239 |
| <45 | 179 | 8 | 4.5 | 1.64 | 178 | 4 | 2.2 | 0.82 | 0.47 | (0.14, 1.56) | 0.2160 | |
| >=45 | 1009 | 29 | 2.9 | 1.02 | 993 | 18 | 1.8 | 0.63 | 0.65 | (0.36, 1.18) | 0.1594 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.5445 |
| Normal (<30) | 250 | 15 | 6.0 | 2.09 | 257 | 6 | 2.3 | 0.81 | 0.40 | (0.16, 1.04) | 0.0612 | |
| Microalbuminuria (30 to <=300) | 675 | 13 | 1.9 | 0.68 | 645 | 9 | 1.4 | 0.49 | 0.79 | (0.34, 1.87) | 0.5980 | |
| Macroalbuminuria (>300) | 260 | 9 | 3.5 | 1.32 | 261 | 7 | 2.7 | 0.96 | 0.73 | (0.27, 1.97) | 0.5359 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5316 |
| Low, moderate or high | 1018 | 31 | 3.0 | 1.08 | 1001 | 17 | 1.7 | 0.59 | 0.57 | (0.31, 1.02) | 0.0602 | |
| Very high | 167 | 6 | 3.6 | 1.34 | 162 | 5 | 3.1 | 1.16 | 0.87 | (0.26, 2.84) | 0.8109 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.4358 |
| No | 205 | 6 | 2.9 | 1.03 | 211 | 2 | 0.9 | 0.32 | 0.34 | (0.07, 1.71) | 0.1919 | |
| Yes | 983 | 31 | 3.2 | 1.13 | 960 | 20 | 2.1 | 0.74 | 0.68 | (0.38, 1.19) | 0.1739 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.0870 |
| No | 422 | 14 | 3.3 | 1.20 | 408 | 4 | 1.0 | 0.35 | 0.28 | (0.09, 0.85) | 0.0242 | |
| Yes | 766 | 23 | 3.0 | 1.07 | 763 | 18 | 2.4 | 0.82 | 0.85 | (0.46, 1.57) | 0.5954 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.0853 |
| No | 629 | 11 | 1.7 | 0.62 | 589 | 2 | 0.3 | 0.12 | 0.19 | (0.04, 0.86) | 0.0312 | |
| Yes | 559 | 26 | 4.7 | 1.69 | 582 | 20 | 3.4 | 1.24 | 0.79 | (0.44, 1.42) | 0.4261 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 18.0.

**Figure R.4.1.1.2.14: 1**

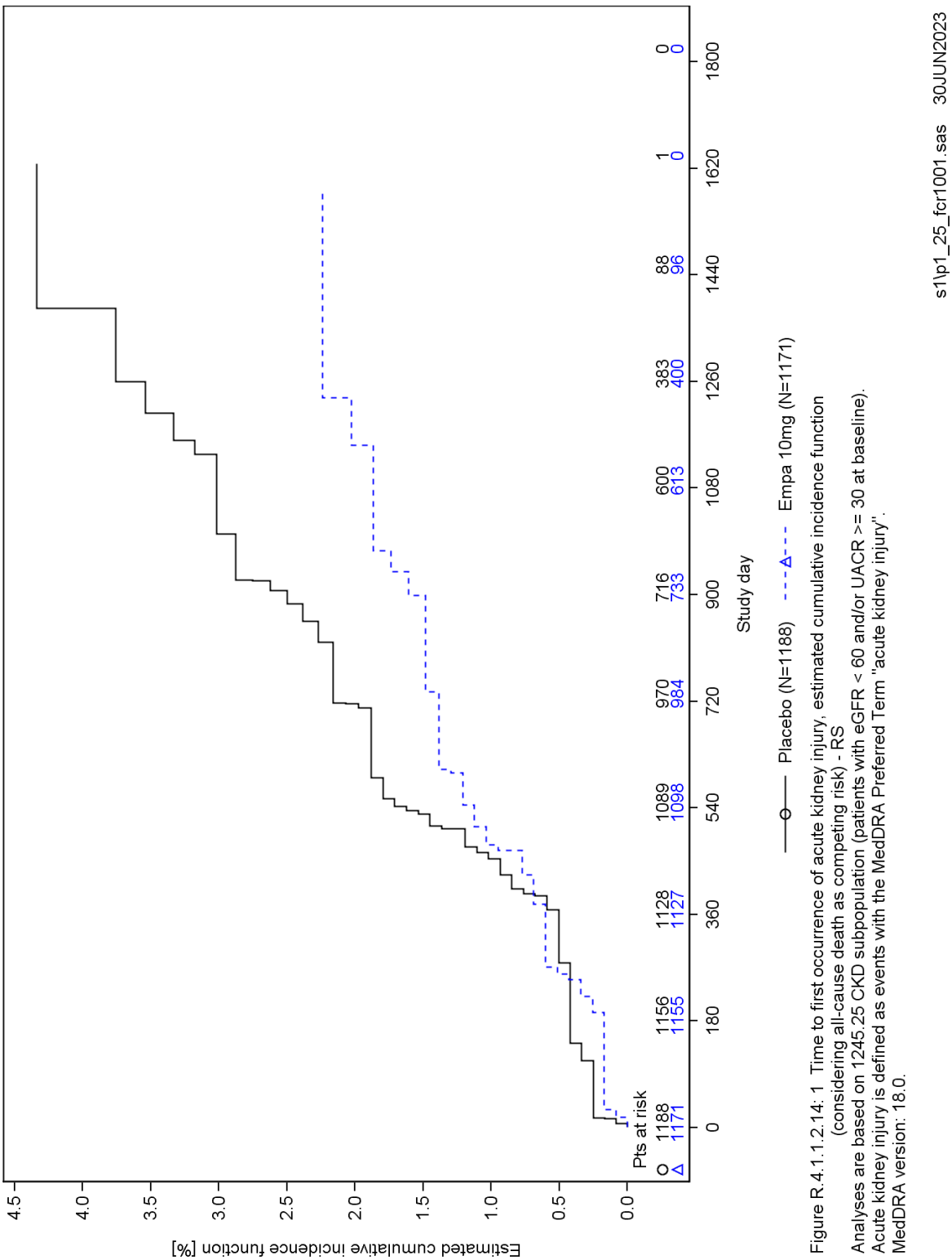


Figure R.4.1.1.2.14: 1 Time to first occurrence of acute kidney injury, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 18.0.

**R.4.1.1.3**

R.4.1.1.3.1 Time to first occurrence of an adjudicated major cardiovascular event

Table R.4.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1188 | 220 | 18.5 | 7.03 | 1171 | 176 | 15.0 | 5.53 | 0.79 | (0.65,0.96) | 0.0184 | |
| Sex | | | | | | | | | | | | 0.8330 |
| Male | 864 | 164 | 19.0 | 7.20 | 837 | 130 | 15.5 | 5.72 | 0.80 | (0.63,1.00) | 0.0546 | |
| Female | 324 | 56 | 17.3 | 6.57 | 334 | 46 | 13.8 | 5.03 | 0.76 | (0.51,1.12) | 0.1678 | |
| Age [years] | | | | | | | | | | | | 0.2234 |
| <65 | 569 | 90 | 15.8 | 5.84 | 547 | 81 | 14.8 | 5.27 | 0.90 | (0.67,1.22) | 0.5112 | |
| >=65 | 619 | 130 | 21.0 | 8.17 | 624 | 95 | 15.2 | 5.76 | 0.70 | (0.54,0.92) | 0.0097 | |
| Region | | | | | | | | | | | | 0.2215 |
| Europe | 468 | 83 | 17.7 | 6.66 | 434 | 78 | 18.0 | 6.78 | 1.02 | (0.75,1.39) | 0.8845 | |
| North America | 259 | 48 | 18.5 | 7.24 | 241 | 27 | 11.2 | 4.15 | 0.58 | (0.36,0.94) | 0.0256 | |
| Latin America | 177 | 35 | 19.8 | 7.81 | 191 | 28 | 14.7 | 5.43 | 0.67 | (0.40,1.09) | 0.1088 | |
| Africa | 50 | 13 | 26.0 | 10.45 | 54 | 8 | 14.8 | 5.56 | 0.50 | (0.21,1.21) | 0.1265 | |
| Asia | 234 | 41 | 17.5 | 6.30 | 251 | 35 | 13.9 | 4.83 | 0.78 | (0.50,1.23) | 0.2873 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1907 |
| <30 | 554 | 109 | 19.7 | 7.36 | 566 | 79 | 14.0 | 5.05 | 0.68 | (0.51,0.92) | 0.0105 | |
| >=30 | 634 | 111 | 17.5 | 6.73 | 605 | 97 | 16.0 | 5.98 | 0.89 | (0.68,1.17) | 0.4172 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7585 |
| <130 | 379 | 70 | 18.5 | 6.97 | 382 | 53 | 13.9 | 5.11 | 0.75 | (0.53,1.07) | 0.1177 | |
| >=130 | 809 | 150 | 18.5 | 7.05 | 789 | 123 | 15.6 | 5.73 | 0.80 | (0.63,1.02) | 0.0737 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2640 |
| <75 | 500 | 90 | 18.0 | 6.73 | 500 | 73 | 14.6 | 5.25 | 0.79 | (0.58,1.08) | 0.1434 | |
| 75 to <85 | 427 | 84 | 19.7 | 7.59 | 417 | 56 | 13.4 | 4.98 | 0.66 | (0.47,0.92) | 0.0148 | |
| >=85 | 261 | 46 | 17.6 | 6.69 | 254 | 47 | 18.5 | 7.01 | 1.02 | (0.68,1.53) | 0.9217 | |
| History of heart failure | | | | | | | | | | | | 0.6363 |
| No | 1048 | 170 | 16.2 | 6.01 | 1031 | 137 | 13.3 | 4.79 | 0.80 | (0.64,1.00) | 0.0489 | |
| Yes | 140 | 50 | 35.7 | 16.57 | 140 | 39 | 27.9 | 11.96 | 0.71 | (0.47,1.08) | 0.1108 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent Mis), adjudicated stroke or adjudicated hospitalization for heart failure.

Table R.4.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8502 |
| <45 | 179 | 38 | 21.2 | 8.27 | 178 | 29 | 16.3 | 6.22 | 0.76 | (0.47,1.23) | 0.2602 | |
| >=45 | 1009 | 182 | 18.0 | 6.81 | 993 | 147 | 14.8 | 5.41 | 0.80 | (0.64,0.99) | 0.0409 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2685 |
| Normal (<30) | 250 | 36 | 14.4 | 5.17 | 257 | 39 | 15.2 | 5.49 | 1.06 | (0.67,1.67) | 0.7941 | |
| Microalbuminuria (30 to <=300) | 675 | 111 | 16.4 | 6.13 | 645 | 81 | 12.6 | 4.59 | 0.76 | (0.57,1.01) | 0.0589 | |
| Macroalbuminuria (>300) | 260 | 73 | 28.1 | 11.80 | 261 | 54 | 20.7 | 7.81 | 0.66 | (0.47,0.94) | 0.0224 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7385 |
| Low, moderate or high | 1018 | 176 | 17.3 | 6.47 | 1001 | 141 | 14.1 | 5.12 | 0.80 | (0.64,0.99) | 0.0445 | |
| Very high | 167 | 44 | 26.3 | 10.87 | 162 | 33 | 20.4 | 8.00 | 0.73 | (0.47,1.15) | 0.1740 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7633 |
| No | 205 | 34 | 16.6 | 6.04 | 211 | 30 | 14.2 | 5.11 | 0.84 | (0.52,1.38) | 0.4997 | |
| Yes | 983 | 186 | 18.9 | 7.24 | 960 | 146 | 15.2 | 5.62 | 0.78 | (0.63,0.97) | 0.0229 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6179 |
| No | 422 | 65 | 15.4 | 5.74 | 408 | 55 | 13.5 | 4.94 | 0.85 | (0.59,1.22) | 0.3698 | |
| Yes | 766 | 155 | 20.2 | 7.75 | 763 | 121 | 15.9 | 5.84 | 0.76 | (0.60,0.96) | 0.0239 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.8118 |
| No | 629 | 89 | 14.1 | 5.25 | 589 | 66 | 11.2 | 3.97 | 0.75 | (0.55,1.04) | 0.0827 | |
| Yes | 559 | 131 | 23.4 | 9.13 | 582 | 110 | 18.9 | 7.21 | 0.79 | (0.61,1.02) | 0.0726 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent Mis), adjudicated stroke or adjudicated hospitalization for heart failure.

**Figure R.4.1.1.3.1: 1**

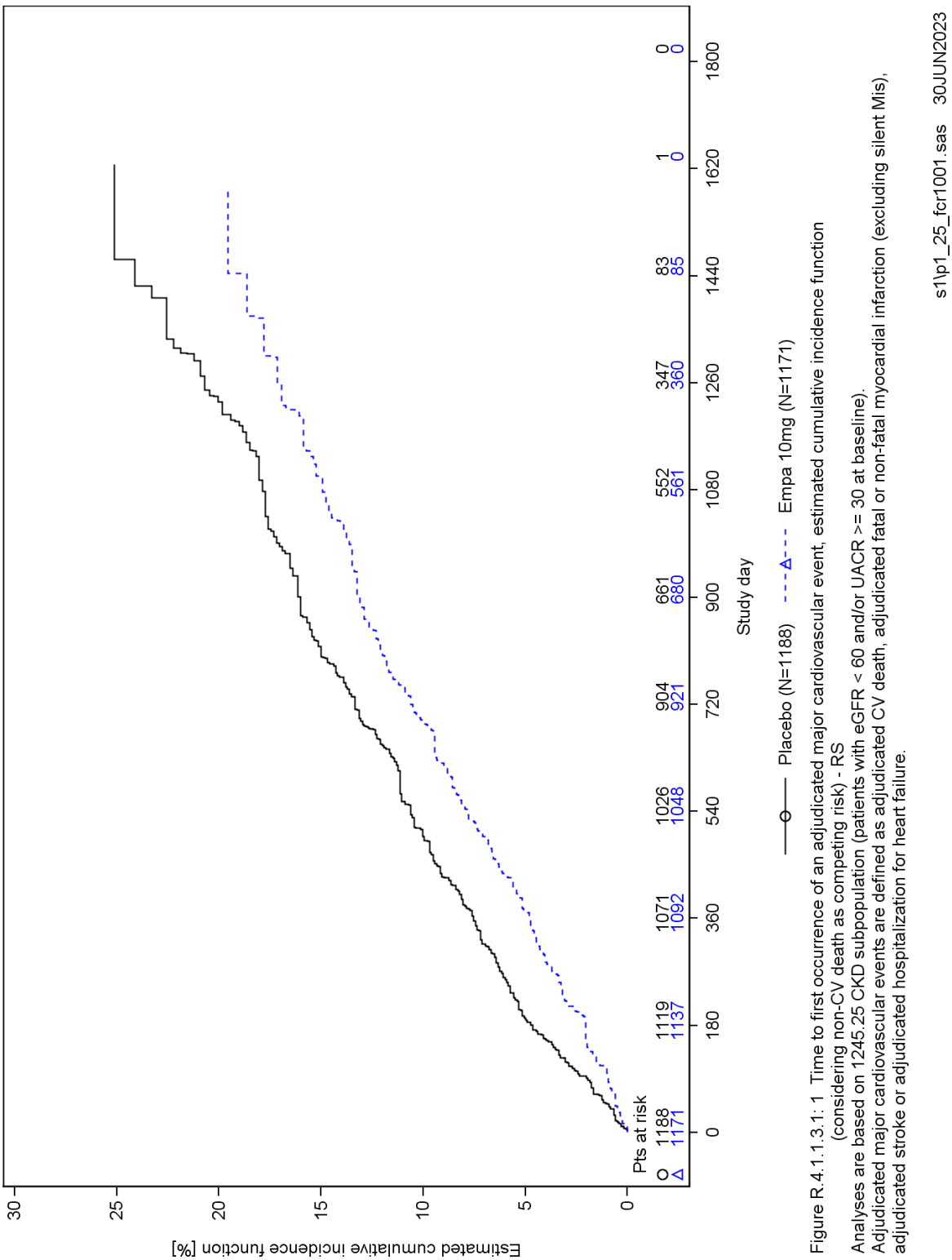


Figure R.4.1.1.3.1: 1 Time to first occurrence of an adjudicated major cardiovascular event, estimated cumulative incidence function (considering non-CV death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent Mis), adjudicated stroke or adjudicated hospitalization for heart failure.

R.4.1.1.3.2 Time to first occurrence of an adjudicated myocardial infarction

Table R.4.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1188 | 77 | 6.5 | 2.35 | 1171 | 62 | 5.3 | 1.88 | 0.81 | (0.58,1.13) | 0.2160 | |
| Sex | | | | | | | | | | | | 0.3357 |
| Male | 864 | 54 | 6.3 | 2.27 | 837 | 47 | 5.6 | 2.00 | 0.90 | (0.61,1.32) | 0.5808 | |
| Female | 324 | 23 | 7.1 | 2.59 | 334 | 15 | 4.5 | 1.59 | 0.62 | (0.32,1.18) | 0.1455 | |
| Age [years] | | | | | | | | | | | | 0.2402 |
| <65 | 569 | 28 | 4.9 | 1.75 | 547 | 28 | 5.1 | 1.76 | 1.03 | (0.61,1.74) | 0.9177 | |
| >=65 | 619 | 49 | 7.9 | 2.93 | 624 | 34 | 5.4 | 2.00 | 0.68 | (0.44,1.06) | 0.0876 | |
| Region | | | | | | | | | | | | 0.6995 |
| Europe | 468 | 33 | 7.1 | 2.55 | 434 | 22 | 5.1 | 1.83 | 0.72 | (0.42,1.24) | 0.2423 | |
| North America | 259 | 21 | 8.1 | 2.98 | 241 | 12 | 5.0 | 1.80 | 0.62 | (0.30,1.26) | 0.1840 | |
| Latin America | 177 | 8 | 4.5 | 1.70 | 191 | 11 | 5.8 | 2.09 | 1.18 | (0.48,2.94) | 0.7178 | |
| Africa | 50 | 5 | 10.0 | 3.73 | 54 | 4 | 7.4 | 2.75 | 0.70 | (0.19,2.63) | 0.6021 | |
| Asia | 234 | 10 | 4.3 | 1.50 | 251 | 13 | 5.2 | 1.74 | 1.17 | (0.51,2.67) | 0.7068 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7271 |
| <30 | 554 | 33 | 6.0 | 2.15 | 566 | 26 | 4.6 | 1.61 | 0.76 | (0.45,1.26) | 0.2846 | |
| >=30 | 634 | 44 | 6.9 | 2.54 | 605 | 36 | 6.0 | 2.15 | 0.85 | (0.55,1.32) | 0.4764 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3840 |
| <130 | 379 | 21 | 5.5 | 2.00 | 382 | 21 | 5.5 | 1.97 | 1.01 | (0.55,1.86) | 0.9668 | |
| >=130 | 809 | 56 | 6.9 | 2.52 | 789 | 41 | 5.2 | 1.84 | 0.73 | (0.49,1.10) | 0.1314 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.1653 |
| <75 | 500 | 31 | 6.2 | 2.22 | 500 | 28 | 5.6 | 1.96 | 0.91 | (0.54,1.51) | 0.7092 | |
| 75 to <85 | 427 | 37 | 8.7 | 3.23 | 417 | 21 | 5.0 | 1.80 | 0.57 | (0.33,0.98) | 0.0412 | |
| >=85 | 261 | 9 | 3.4 | 1.24 | 254 | 13 | 5.1 | 1.86 | 1.45 | (0.62,3.40) | 0.3920 | |
| History of heart failure | | | | | | | | | | | | 0.0415 |
| No | 1048 | 57 | 5.4 | 1.95 | 1031 | 54 | 5.2 | 1.84 | 0.96 | (0.66,1.39) | 0.8286 | |
| Yes | 140 | 20 | 14.3 | 5.78 | 140 | 8 | 5.7 | 2.27 | 0.38 | (0.16,0.85) | 0.0193 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

Table R.4.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.9115 |
| <45 | 179 | 15 | 8.4 | 3.10 | 178 | 13 | 7.3 | 2.69 | 0.84 | (0.40,1.77) | 0.6430 | |
| >=45 | 1009 | 62 | 6.1 | 2.22 | 993 | 49 | 4.9 | 1.74 | 0.80 | (0.55,1.16) | 0.2435 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7238 |
| Normal (<30) | 250 | 16 | 6.4 | 2.24 | 257 | 11 | 4.3 | 1.50 | 0.66 | (0.31,1.43) | 0.2956 | |
| Microalbuminuria (30 to <=300) | 675 | 42 | 6.2 | 2.23 | 645 | 36 | 5.6 | 1.98 | 0.92 | (0.59,1.44) | 0.7236 | |
| Macroalbuminuria (>300) | 260 | 19 | 7.3 | 2.84 | 261 | 15 | 5.7 | 2.09 | 0.74 | (0.38,1.46) | 0.3852 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5307 |
| Low, moderate or high | 1018 | 64 | 6.3 | 2.26 | 1001 | 49 | 4.9 | 1.72 | 0.77 | (0.53,1.12) | 0.1770 | |
| Very high | 167 | 13 | 7.8 | 2.96 | 162 | 13 | 8.0 | 3.04 | 1.02 | (0.47,2.19) | 0.9659 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6078 |
| No | 205 | 15 | 7.3 | 2.61 | 211 | 15 | 7.1 | 2.48 | 0.95 | (0.47,1.95) | 0.8962 | |
| Yes | 983 | 62 | 6.3 | 2.30 | 960 | 47 | 4.9 | 1.75 | 0.77 | (0.53,1.13) | 0.1791 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.7856 |
| No | 422 | 21 | 5.0 | 1.81 | 408 | 18 | 4.4 | 1.58 | 0.87 | (0.46,1.63) | 0.6647 | |
| Yes | 766 | 56 | 7.3 | 2.65 | 763 | 44 | 5.8 | 2.04 | 0.78 | (0.53,1.16) | 0.2288 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2247 |
| No | 629 | 37 | 5.9 | 2.13 | 589 | 22 | 3.7 | 1.30 | 0.63 | (0.37,1.06) | 0.0821 | |
| Yes | 559 | 40 | 7.2 | 2.62 | 582 | 40 | 6.9 | 2.51 | 0.96 | (0.62,1.49) | 0.8476 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

**Figure R.4.1.1.3.2: 1**

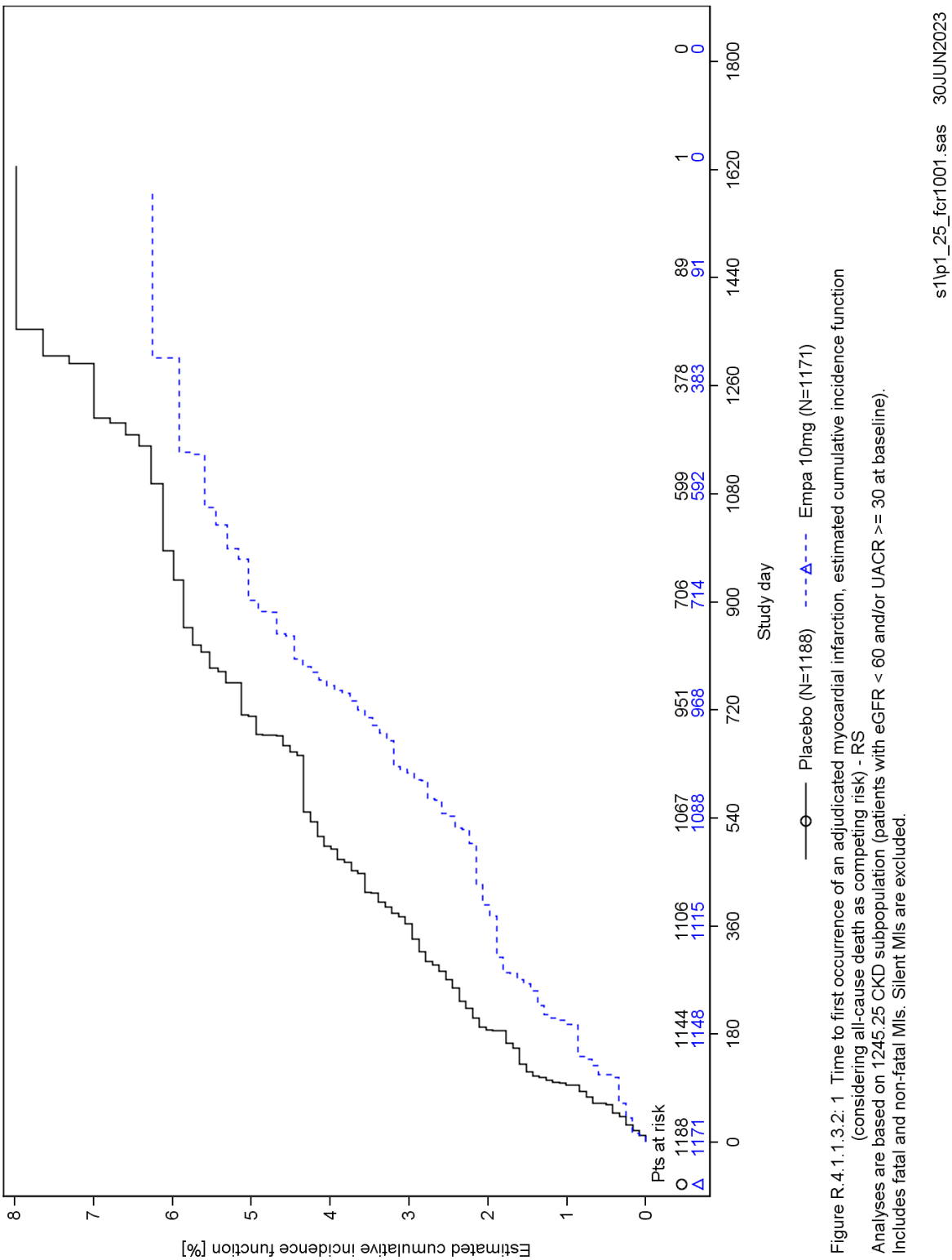


Figure R.4.1.1.3.2: 1 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

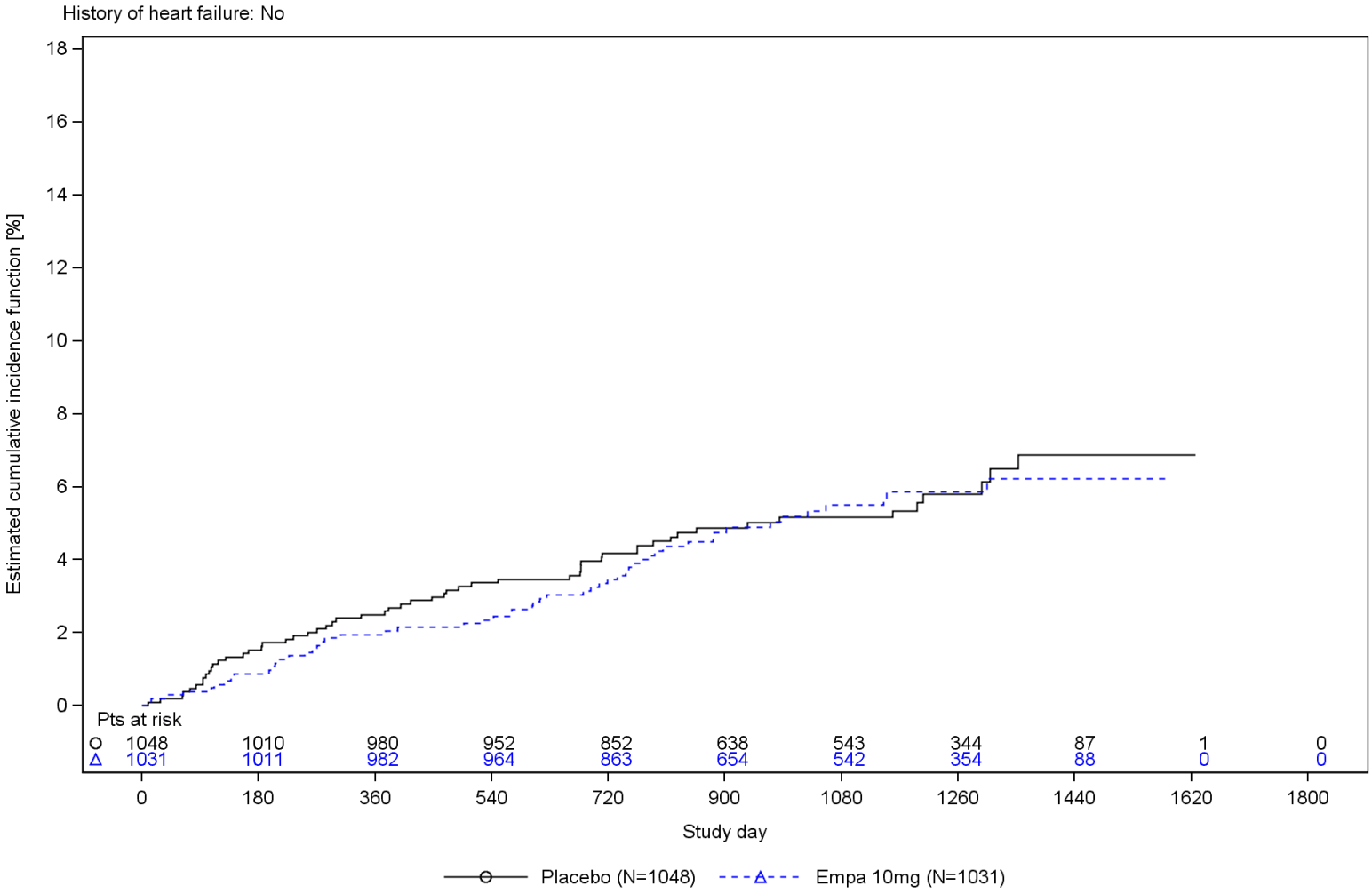


Figure R.4.1.1.3.2: 2 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: history of heart failure - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

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**Figure R.4.1.1.3.2: 2**

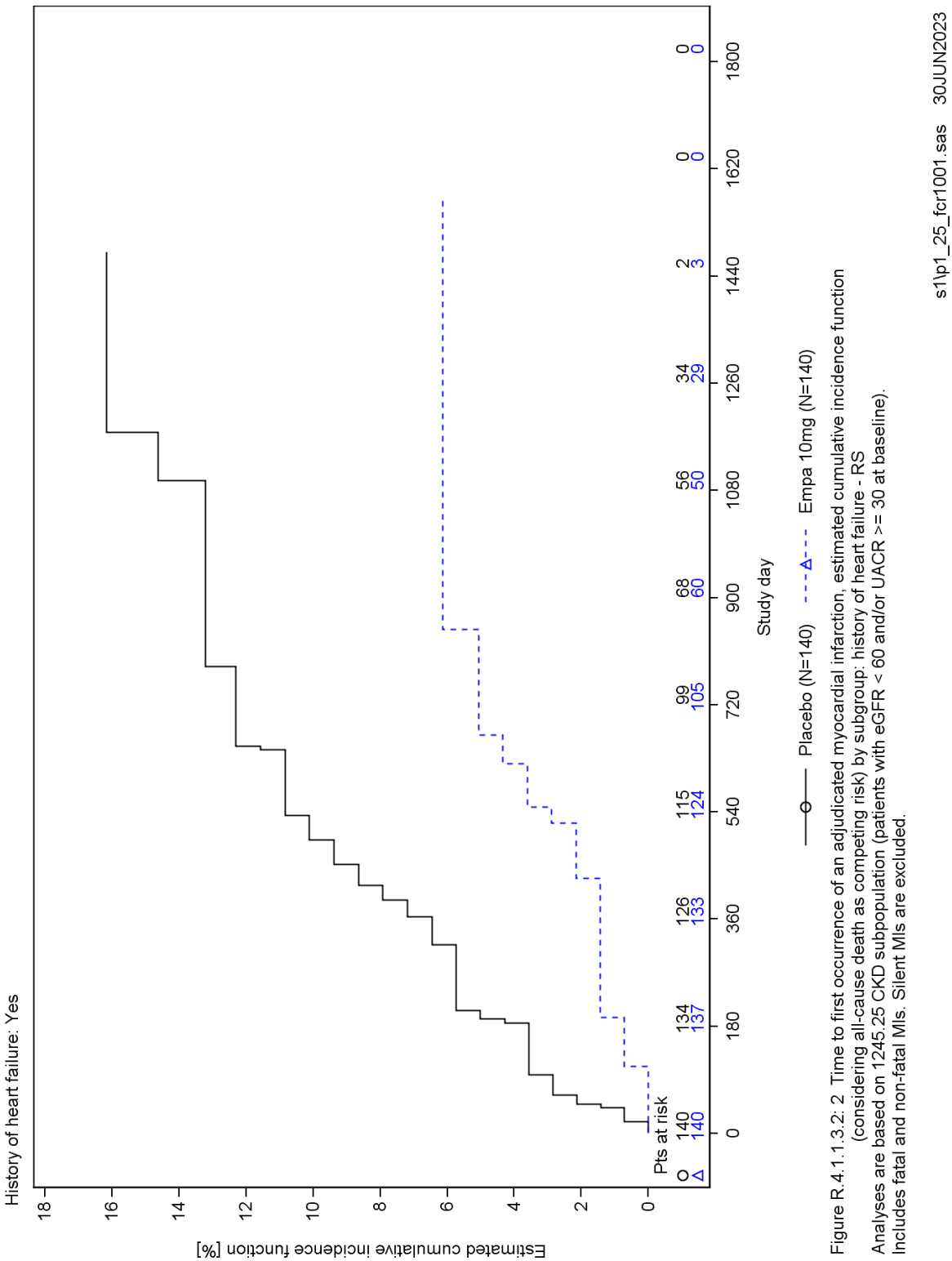


Figure R.4.1.1.3.2: 2 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: history of heart failure - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

R.4.1.1.3.3 Time to first occurrence of an adjudicated stroke

Table R.4.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1188 | 46 | 3.9 | 1.40 | 1171 | 52 | 4.4 | 1.57 | 1.12 | (0.76,1.67) | 0.5616 | |
| Sex | | | | | | | | | | | | 0.7603 |
| Male | 864 | 33 | 3.8 | 1.38 | 837 | 38 | 4.5 | 1.61 | 1.17 | (0.73,1.86) | 0.5133 | |
| Female | 324 | 13 | 4.0 | 1.45 | 334 | 14 | 4.2 | 1.48 | 1.02 | (0.48,2.17) | 0.9641 | |
| Age [years] | | | | | | | | | | | | 0.3441 |
| <65 | 569 | 17 | 3.0 | 1.06 | 547 | 24 | 4.4 | 1.52 | 1.40 | (0.75,2.62) | 0.2843 | |
| >=65 | 619 | 29 | 4.7 | 1.72 | 624 | 28 | 4.5 | 1.63 | 0.95 | (0.56,1.60) | 0.8456 | |
| Region | | | | | | | | | | | | 0.0529 |
| Europe | 468 | 12 | 2.6 | 0.91 | 434 | 26 | 6.0 | 2.17 | 2.39 | (1.20,4.74) | 0.0127 | |
| North America | 259 | 11 | 4.2 | 1.58 | 241 | 6 | 2.5 | 0.90 | 0.56 | (0.21,1.53) | 0.2609 | |
| Latin America | 177 | 8 | 4.5 | 1.67 | 191 | 5 | 2.6 | 0.93 | 0.56 | (0.18,1.72) | 0.3110 | |
| Africa | 50 | 3 | 6.0 | 2.20 | 54 | 1 | 1.9 | 0.66 | 0.29 | (0.03,2.82) | 0.2887 | |
| Asia | 234 | 12 | 5.1 | 1.82 | 251 | 14 | 5.6 | 1.88 | 1.05 | (0.48,2.26) | 0.9105 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.4654 |
| <30 | 554 | 25 | 4.5 | 1.62 | 566 | 33 | 5.8 | 2.06 | 1.27 | (0.76,2.14) | 0.3627 | |
| >=30 | 634 | 21 | 3.3 | 1.20 | 605 | 19 | 3.1 | 1.12 | 0.94 | (0.51,1.75) | 0.8495 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8516 |
| <130 | 379 | 10 | 2.6 | 0.95 | 382 | 12 | 3.1 | 1.11 | 1.20 | (0.52,2.79) | 0.6673 | |
| >=130 | 809 | 36 | 4.4 | 1.61 | 789 | 40 | 5.1 | 1.80 | 1.10 | (0.70,1.72) | 0.6852 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.8718 |
| <75 | 500 | 14 | 2.8 | 1.00 | 500 | 18 | 3.6 | 1.25 | 1.29 | (0.64,2.60) | 0.4740 | |
| 75 to <85 | 427 | 19 | 4.4 | 1.63 | 417 | 21 | 5.0 | 1.81 | 1.10 | (0.59,2.04) | 0.7719 | |
| >=85 | 261 | 13 | 5.0 | 1.81 | 254 | 13 | 5.1 | 1.85 | 0.98 | (0.45,2.12) | 0.9637 | |
| History of heart failure | | | | | | | | | | | | 0.8968 |
| No | 1048 | 41 | 3.9 | 1.40 | 1031 | 46 | 4.5 | 1.56 | 1.11 | (0.73,1.70) | 0.6149 | |
| Yes | 140 | 5 | 3.6 | 1.38 | 140 | 6 | 4.3 | 1.66 | 1.21 | (0.37,3.98) | 0.7518 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.9168 |
| <45 | 179 | 8 | 4.5 | 1.63 | 178 | 8 | 4.5 | 1.66 | 1.07 | (0.40,2.87) | 0.8886 | |
| >=45 | 1009 | 38 | 3.8 | 1.36 | 993 | 44 | 4.4 | 1.56 | 1.14 | (0.74,1.75) | 0.5654 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.4.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7267 |
| Normal (<30) | 250 | 9 | 3.6 | 1.25 | 257 | 10 | 3.9 | 1.35 | 1.11 | (0.45,2.74) | 0.8166 | |
| Microalbuminuria (30 to <=300) | 675 | 21 | 3.1 | 1.11 | 645 | 26 | 4.0 | 1.43 | 1.27 | (0.71,2.26) | 0.4141 | |
| Macroalbuminuria (>300) | 260 | 16 | 6.2 | 2.38 | 261 | 15 | 5.7 | 2.08 | 0.88 | (0.43,1.78) | 0.7148 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4552 |
| Low, moderate or high | 1018 | 37 | 3.6 | 1.30 | 1001 | 44 | 4.4 | 1.54 | 1.18 | (0.76,1.84) | 0.4485 | |
| Very high | 167 | 9 | 5.4 | 2.05 | 162 | 7 | 4.3 | 1.63 | 0.78 | (0.29,2.11) | 0.6304 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5165 |
| No | 205 | 9 | 4.4 | 1.56 | 211 | 8 | 3.8 | 1.30 | 0.84 | (0.33,2.19) | 0.7288 | |
| Yes | 983 | 37 | 3.8 | 1.36 | 960 | 44 | 4.6 | 1.64 | 1.20 | (0.77,1.85) | 0.4238 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4230 |
| No | 422 | 15 | 3.6 | 1.29 | 408 | 21 | 5.1 | 1.85 | 1.40 | (0.72,2.71) | 0.3245 | |
| Yes | 766 | 31 | 4.0 | 1.46 | 763 | 31 | 4.1 | 1.43 | 0.99 | (0.60,1.64) | 0.9824 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.8597 |
| No | 629 | 24 | 3.8 | 1.37 | 589 | 26 | 4.4 | 1.53 | 1.08 | (0.62,1.89) | 0.7756 | |
| Yes | 559 | 22 | 3.9 | 1.43 | 582 | 26 | 4.5 | 1.62 | 1.17 | (0.66,2.06) | 0.5989 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.3: 1**

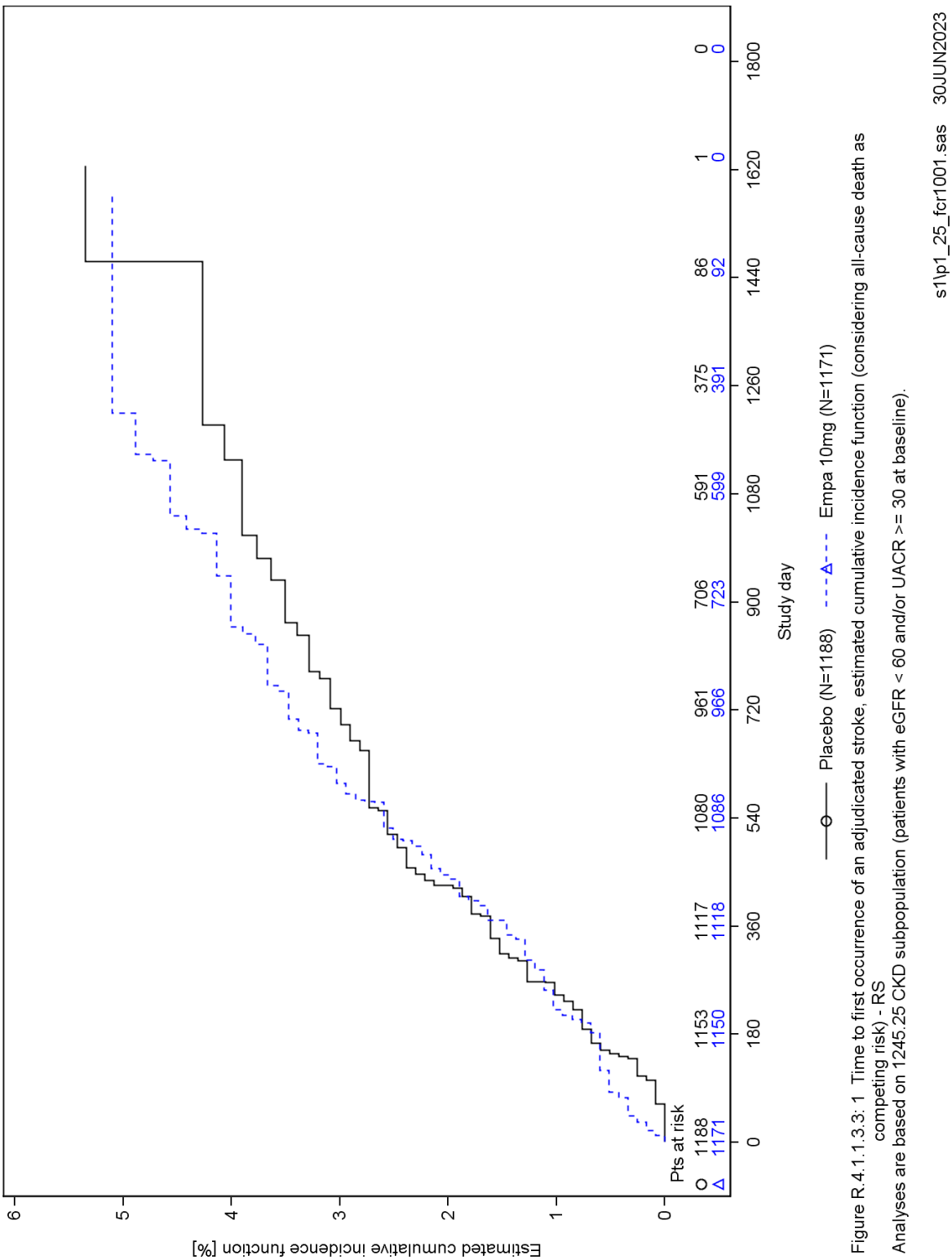


Figure R.4.1.1.3.3: 1 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.4.1.1.3.4 Time to first adjudicated hospitalization for heart failure

Table R.4.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 75 | 6.3 | 2.30 | 1171 | 39 | 3.3 | 1.17 | 0.52 | (0.35,0.77) | 0.0010 | |
| Sex | | | | | | | | | | | | 0.6123 |
| Male | 864 | 50 | 5.8 | 2.11 | 837 | 27 | 3.2 | 1.14 | 0.56 | (0.35,0.89) | 0.0148 | |
| Female | 324 | 25 | 7.7 | 2.80 | 334 | 12 | 3.6 | 1.27 | 0.45 | (0.23,0.90) | 0.0231 | |
| Age [years] | | | | | | | | | | | | 0.8729 |
| <65 | 569 | 27 | 4.7 | 1.70 | 547 | 14 | 2.6 | 0.87 | 0.54 | (0.28,1.02) | 0.0579 | |
| >=65 | 619 | 48 | 7.8 | 2.86 | 624 | 25 | 4.0 | 1.46 | 0.50 | (0.31,0.81) | 0.0052 | |
| Region | | | | | | | | | | | | 0.1383 |
| Europe | 468 | 31 | 6.6 | 2.40 | 434 | 22 | 5.1 | 1.83 | 0.78 | (0.45,1.35) | 0.3812 | |
| North America | 259 | 17 | 6.6 | 2.42 | 241 | 4 | 1.7 | 0.59 | 0.25 | (0.08,0.74) | 0.0125 | |
| Latin America | 177 | 9 | 5.1 | 1.92 | 191 | 4 | 2.1 | 0.74 | 0.36 | (0.11,1.18) | 0.0929 | |
| Africa | 50 | 8 | 16.0 | 6.04 | 54 | 1 | 1.9 | 0.66 | 0.10 | (0.01,0.82) | 0.0318 | |
| Asia | 234 | 10 | 4.3 | 1.49 | 251 | 8 | 3.2 | 1.05 | 0.73 | (0.29,1.85) | 0.5094 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0312 |
| <30 | 554 | 31 | 5.6 | 2.02 | 566 | 9 | 1.6 | 0.55 | 0.27 | (0.13,0.57) | 0.0006 | |
| >=30 | 634 | 44 | 6.9 | 2.54 | 605 | 30 | 5.0 | 1.77 | 0.71 | (0.45,1.13) | 0.1473 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0947 |
| <130 | 379 | 31 | 8.2 | 3.01 | 382 | 10 | 2.6 | 0.92 | 0.32 | (0.16,0.65) | 0.0018 | |
| >=130 | 809 | 44 | 5.4 | 1.97 | 789 | 29 | 3.7 | 1.30 | 0.66 | (0.42,1.06) | 0.0885 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2403 |
| <75 | 500 | 39 | 7.8 | 2.83 | 500 | 16 | 3.2 | 1.11 | 0.41 | (0.23,0.74) | 0.0030 | |
| 75 to <85 | 427 | 22 | 5.2 | 1.88 | 417 | 10 | 2.4 | 0.85 | 0.46 | (0.22,0.96) | 0.0393 | |
| >=85 | 261 | 14 | 5.4 | 1.96 | 254 | 13 | 5.1 | 1.86 | 0.91 | (0.43,1.95) | 0.8172 | |
| History of heart failure | | | | | | | | | | | | 0.7972 |
| No | 1048 | 48 | 4.6 | 1.64 | 1031 | 23 | 2.2 | 0.77 | 0.48 | (0.29,0.79) | 0.0040 | |
| Yes | 140 | 27 | 19.3 | 8.20 | 140 | 16 | 11.4 | 4.69 | 0.53 | (0.29,0.99) | 0.0476 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8784 |
| <45 | 179 | 15 | 8.4 | 3.13 | 178 | 8 | 4.5 | 1.64 | 0.49 | (0.21,1.16) | 0.1027 | |
| >=45 | 1009 | 60 | 5.9 | 2.16 | 993 | 31 | 3.1 | 1.09 | 0.53 | (0.34,0.81) | 0.0038 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.4.1.1.3.4: 1

Table R.4.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8612 |
| Normal (<30) | 250 | 12 | 4.8 | 1.66 | 257 | 8 | 3.1 | 1.08 | 0.64 | (0.26,1.56) | 0.3221 | |
| Microalbuminuria (30 to <=300) | 675 | 39 | 5.8 | 2.07 | 645 | 17 | 2.6 | 0.92 | 0.48 | (0.27,0.85) | 0.0118 | |
| Macroalbuminuria (>300) | 260 | 24 | 9.2 | 3.68 | 261 | 13 | 5.0 | 1.81 | 0.48 | (0.25,0.95) | 0.0359 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.6780 |
| Low, moderate or high | 1018 | 55 | 5.4 | 1.94 | 1001 | 29 | 2.9 | 1.01 | 0.53 | (0.34,0.84) | 0.0064 | |
| Very high | 167 | 20 | 12.0 | 4.74 | 162 | 9 | 5.6 | 2.10 | 0.44 | (0.20,0.97) | 0.0416 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5988 |
| No | 205 | 7 | 3.4 | 1.20 | 211 | 5 | 2.4 | 0.81 | 0.70 | (0.22,2.20) | 0.5380 | |
| Yes | 983 | 68 | 6.9 | 2.54 | 960 | 34 | 3.5 | 1.25 | 0.50 | (0.33,0.76) | 0.0011 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9373 |
| No | 422 | 20 | 4.7 | 1.72 | 408 | 10 | 2.5 | 0.87 | 0.51 | (0.24,1.08) | 0.0789 | |
| Yes | 766 | 55 | 7.2 | 2.62 | 763 | 29 | 3.8 | 1.33 | 0.52 | (0.33,0.82) | 0.0049 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.0712 |
| No | 629 | 23 | 3.7 | 1.31 | 589 | 5 | 0.8 | 0.29 | 0.23 | (0.09,0.61) | 0.0030 | |
| Yes | 559 | 52 | 9.3 | 3.46 | 582 | 34 | 5.8 | 2.13 | 0.61 | (0.40,0.94) | 0.0264 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.4: 1**

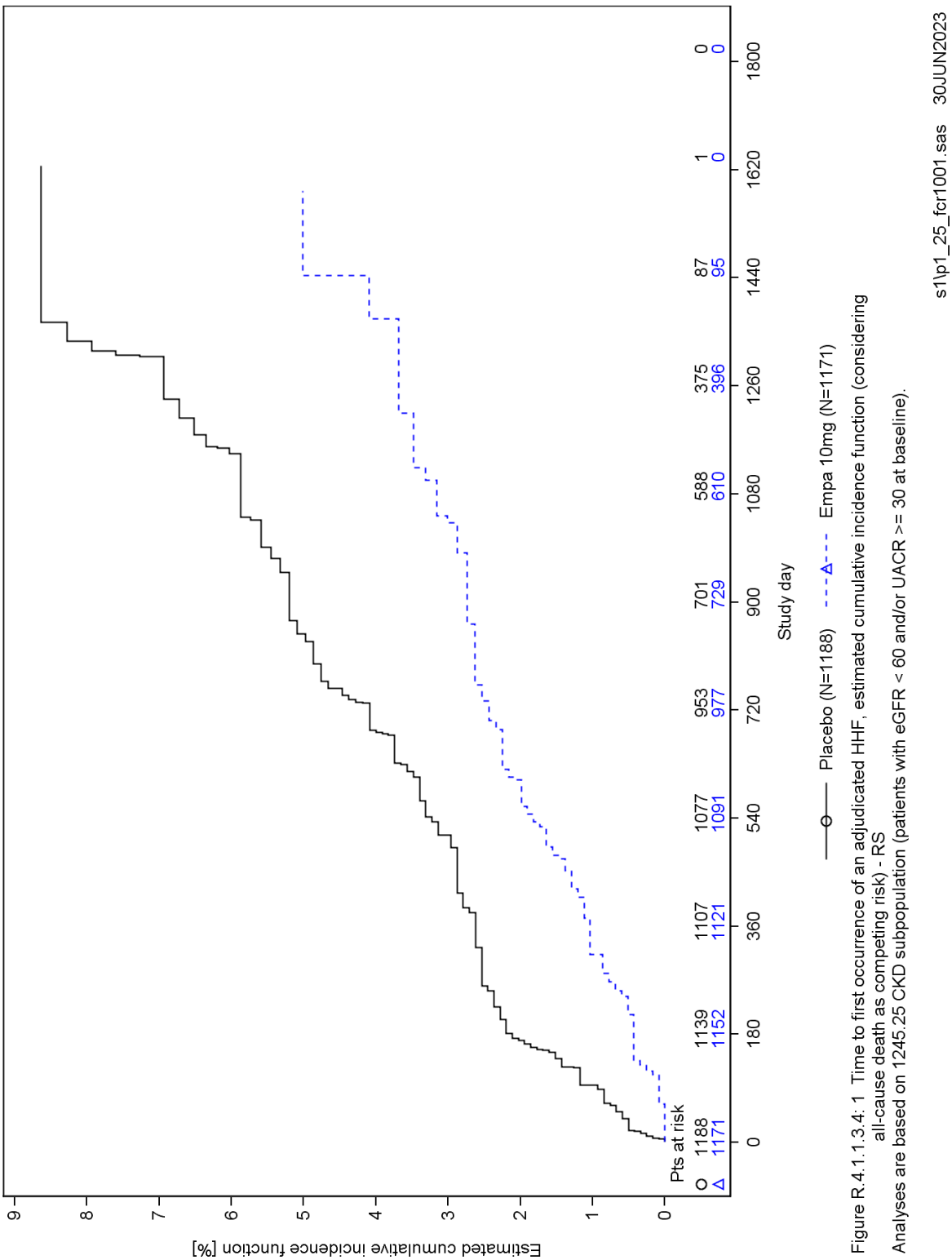


Figure R.4.1.1.3.4: 1 Time to first occurrence of an adjudicated HHF, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.4: 2**

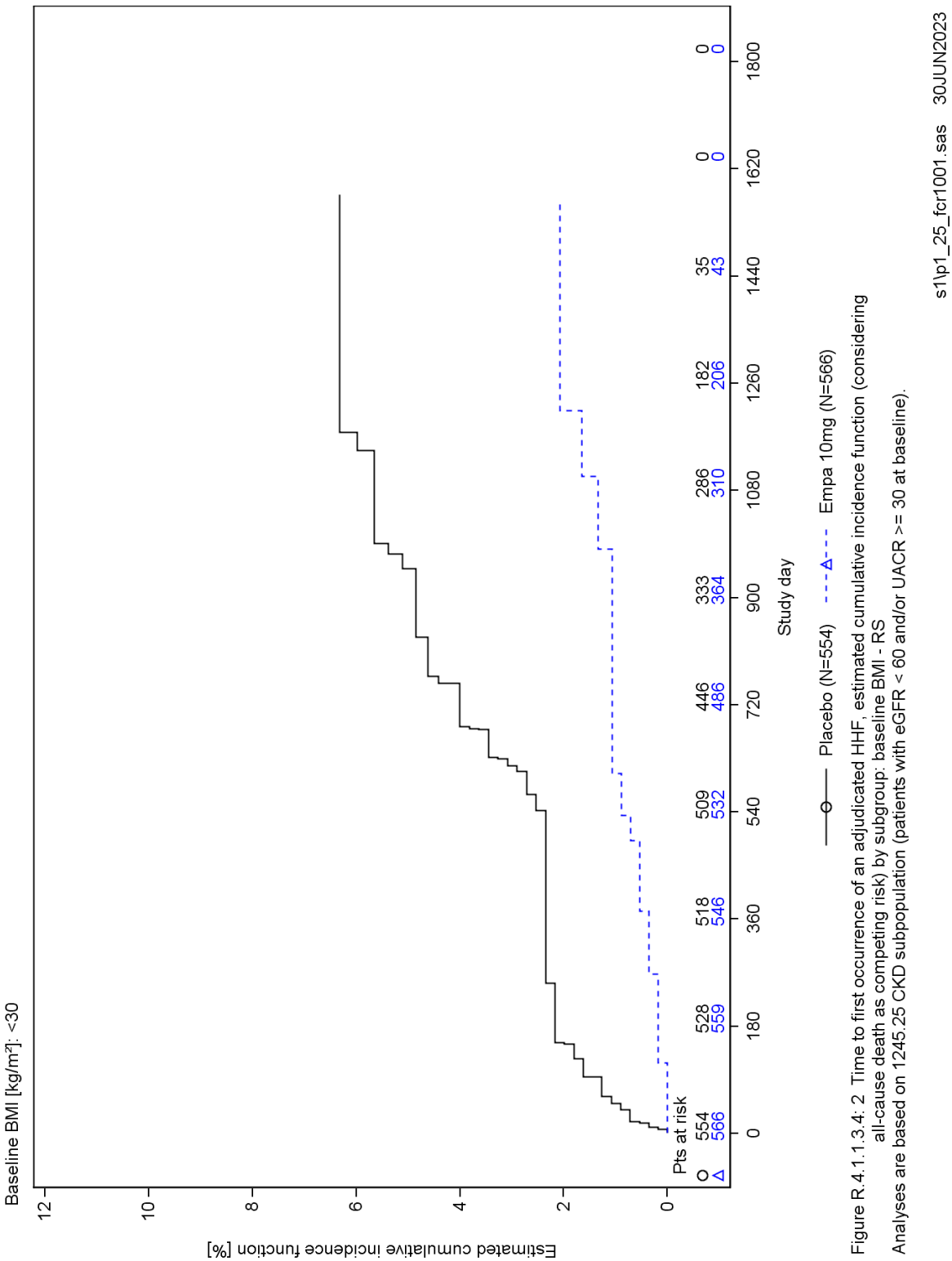


Figure R.4.1.1.3.4: 2 Time to first occurrence of an adjudicated HHF, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline BMI - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.4: 2**

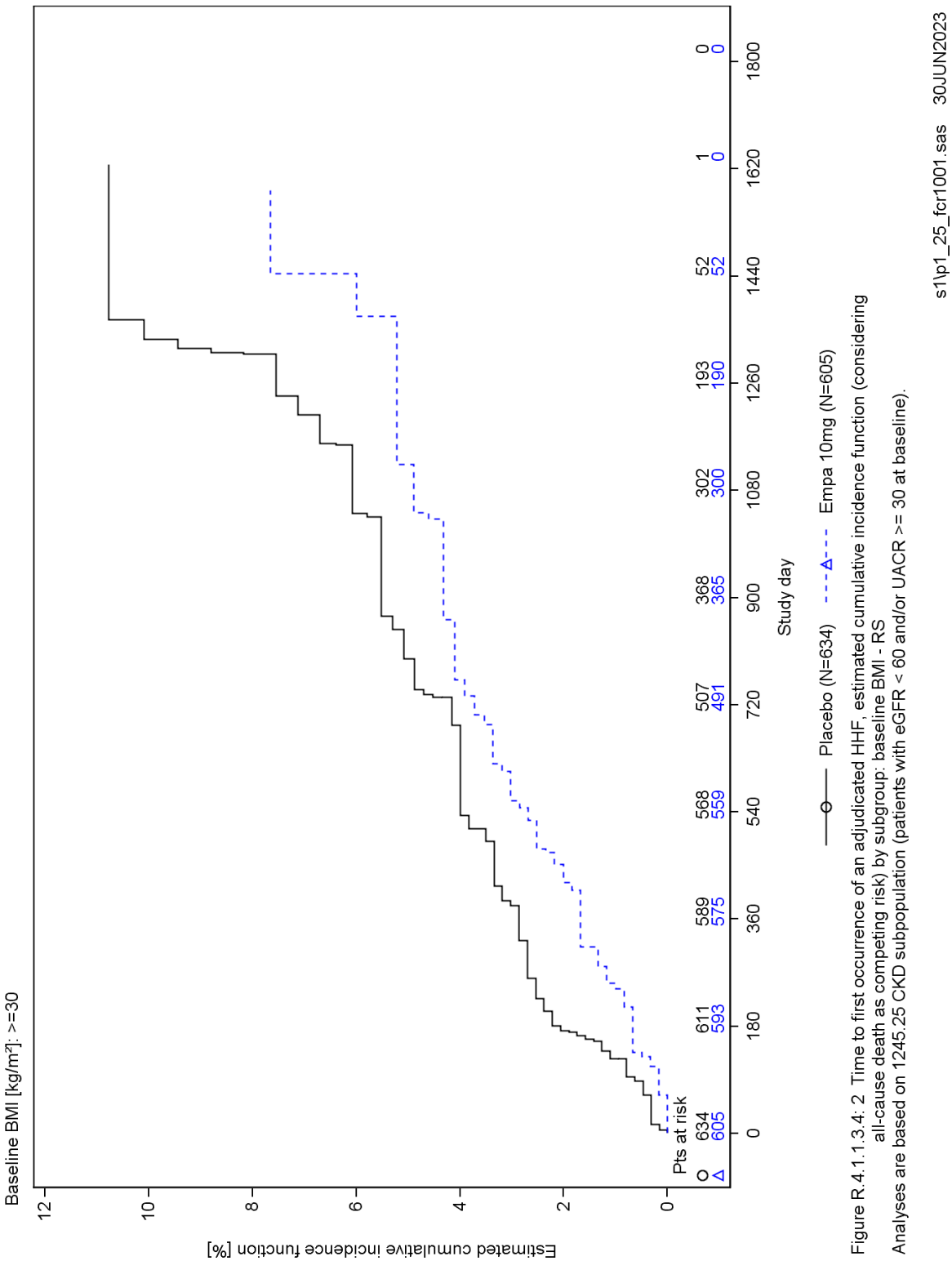


Figure R.4.1.1.3.4: 2 Time to first occurrence of an adjudicated HHF, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline BMI - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.4.1.1.3.5 Time to occurrence of adjudicated hospitalization for heart failure (first and recurrent)

Table R.4.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1188 | 75 | 6.3 | 120 | 3.57 | 1171 | 39 | 3.3 | 58 | 1.72 | 0.40 | ( 0.26,0.61) | <0.0001 | |
| Sex | | | | | | | | | | | | | | 0.7275 |
| Male | 864 | 50 | 5.8 | 80 | 3.27 | 837 | 27 | 3.2 | 35 | 1.45 | 0.42 | ( 0.26,0.70) | 0.0009 | |
| Female | 324 | 25 | 7.7 | 40 | 4.37 | 334 | 12 | 3.6 | 23 | 2.39 | 0.36 | ( 0.17,0.75) | 0.0063 | |
| Age [years] | | | | | | | | | | | | | | 0.9511 |
| <65 | 569 | 27 | 4.7 | 45 | 2.77 | 547 | 14 | 2.6 | 19 | 1.17 | 0.39 | ( 0.20,0.75) | 0.0052 | |
| >=65 | 619 | 48 | 7.8 | 75 | 4.33 | 624 | 25 | 4.0 | 39 | 2.23 | 0.40 | ( 0.23,0.68) | 0.0008 | |
| Region | | | | | | | | | | | | | | 0.1430 |
| Europe | 468 | 31 | 6.6 | 53 | 3.98 | 434 | 22 | 5.1 | 34 | 2.76 | 0.58 | ( 0.32,1.08) | 0.0849 | |
| North America | 259 | 17 | 6.6 | 25 | 3.46 | 241 | 4 | 1.7 | 5 | 0.74 | 0.18 | ( 0.06,0.54) | 0.0022 | |
| Latin America | 177 | 9 | 5.1 | 17 | 3.51 | 191 | 4 | 2.1 | 5 | 0.92 | 0.25 | ( 0.07,0.83) | 0.0231 | |
| Africa | 50 | 8 | 16.0 | 10 | 7.01 | 54 | 1 | 1.9 | 1 | 0.66 | 0.08 | (<0.01,0.87) | 0.0380 | |
| Asia | 234 | 10 | 4.3 | 15 | 2.22 | 251 | 8 | 3.2 | 13 | 1.70 | 0.65 | ( 0.26,1.67) | 0.3750 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0312 |
| <30 | 554 | 31 | 5.6 | 52 | 3.32 | 566 | 9 | 1.6 | 17 | 1.03 | 0.23 | ( 0.12,0.45) | <0.0001 | |
| >=30 | 634 | 44 | 6.9 | 68 | 3.80 | 605 | 30 | 5.0 | 41 | 2.37 | 0.59 | ( 0.34,1.00) | 0.0503 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0532 |
| <130 | 379 | 31 | 8.2 | 51 | 4.77 | 382 | 10 | 2.6 | 13 | 1.18 | 0.22 | ( 0.10,0.48) | 0.0001 | |
| >=130 | 809 | 44 | 5.4 | 69 | 3.01 | 789 | 29 | 3.7 | 45 | 1.98 | 0.54 | ( 0.33,0.89) | 0.0165 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2497 |
| <75 | 500 | 39 | 7.8 | 66 | 4.63 | 500 | 16 | 3.2 | 23 | 1.57 | 0.27 | ( 0.15,0.51) | <0.0001 | |
| 75 to <85 | 427 | 22 | 5.2 | 30 | 2.52 | 417 | 10 | 2.4 | 19 | 1.59 | 0.56 | ( 0.27,1.16) | 0.1195 | |
| >=85 | 261 | 14 | 5.4 | 24 | 3.25 | 254 | 13 | 5.1 | 16 | 2.23 | 0.55 | ( 0.23,1.29) | 0.1707 | |
| History of heart failure | | | | | | | | | | | | | | 0.3367 |
| No | 1048 | 48 | 4.6 | 62 | 2.08 | 1031 | 23 | 2.2 | 37 | 1.23 | 0.50 | ( 0.31,0.81) | 0.0052 | |
| Yes | 140 | 27 | 19.3 | 58 | 15.68 | 140 | 16 | 11.4 | 21 | 5.76 | 0.31 | ( 0.14,0.71) | 0.0055 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline BMI, baseline eGFR (CKD-EPI), baseline HbA1c, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.4.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8528 |
| <45 | 179 | 15 | 8.4 | 29 | 5.82 | 178 | 8 | 4.5 | 13 | 2.63 | 0.38 | ( 0.15,0.96) | 0.0417 | |
| >=45 | 1009 | 60 | 5.9 | 91 | 3.18 | 993 | 31 | 3.1 | 45 | 1.56 | 0.42 | ( 0.26,0.66) | 0.0002 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6217 |
| Normal (<30) | 250 | 12 | 4.8 | 18 | 2.45 | 257 | 8 | 3.1 | 11 | 1.46 | 0.61 | ( 0.24,1.52) | 0.2858 | |
| Microalbuminuria (30 to <=300) | 675 | 39 | 5.8 | 63 | 3.27 | 645 | 17 | 2.6 | 26 | 1.40 | 0.37 | ( 0.20,0.65) | 0.0007 | |
| Macroalbuminuria (>300) | 260 | 24 | 9.2 | 39 | 5.64 | 261 | 13 | 5.0 | 18 | 2.45 | 0.36 | ( 0.17,0.79) | 0.0103 | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4199 |
| Low, moderate or high | 1018 | 55 | 5.4 | 86 | 2.97 | 1001 | 29 | 2.9 | 42 | 1.44 | 0.45 | ( 0.28,0.71) | 0.0006 | |
| Very high | 167 | 20 | 12.0 | 34 | 7.52 | 162 | 9 | 5.6 | 13 | 2.96 | 0.29 | ( 0.12,0.74) | 0.0091 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9625 |
| No | 205 | 7 | 3.4 | 12 | 2.05 | 211 | 5 | 2.4 | 7 | 1.12 | 0.41 | ( 0.13,1.32) | 0.1347 | |
| Yes | 983 | 68 | 6.9 | 108 | 3.90 | 960 | 34 | 3.5 | 51 | 1.86 | 0.40 | ( 0.26,0.63) | <0.0001 | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6344 |
| No | 422 | 20 | 4.7 | 30 | 2.54 | 408 | 10 | 2.5 | 12 | 1.04 | 0.34 | ( 0.15,0.76) | 0.0087 | |
| Yes | 766 | 55 | 7.2 | 90 | 4.13 | 763 | 29 | 3.8 | 46 | 2.08 | 0.42 | ( 0.26,0.69) | 0.0006 | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1883 |
| No | 629 | 23 | 3.7 | 29 | 1.63 | 589 | 5 | 0.8 | 7 | 0.40 | 0.22 | ( 0.09,0.55) | 0.0011 | |
| Yes | 559 | 52 | 9.3 | 91 | 5.79 | 582 | 34 | 5.8 | 51 | 3.11 | 0.44 | ( 0.27,0.73) | 0.0012 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline BMI, baseline eGFR (CKD-EPI), baseline HbA1c, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.5: 1**

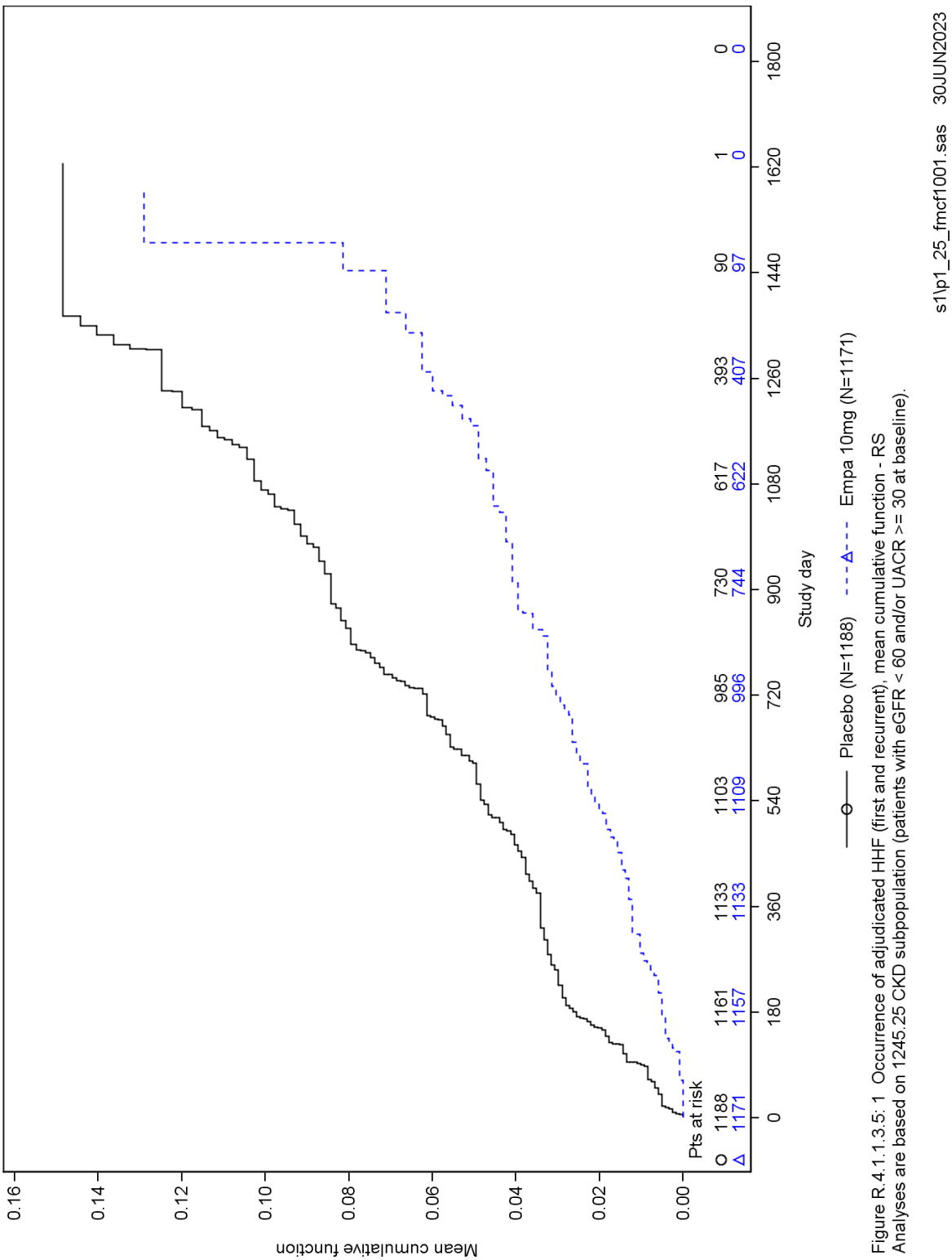


Figure R.4.1.1.3.5: 1 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.5: 2**

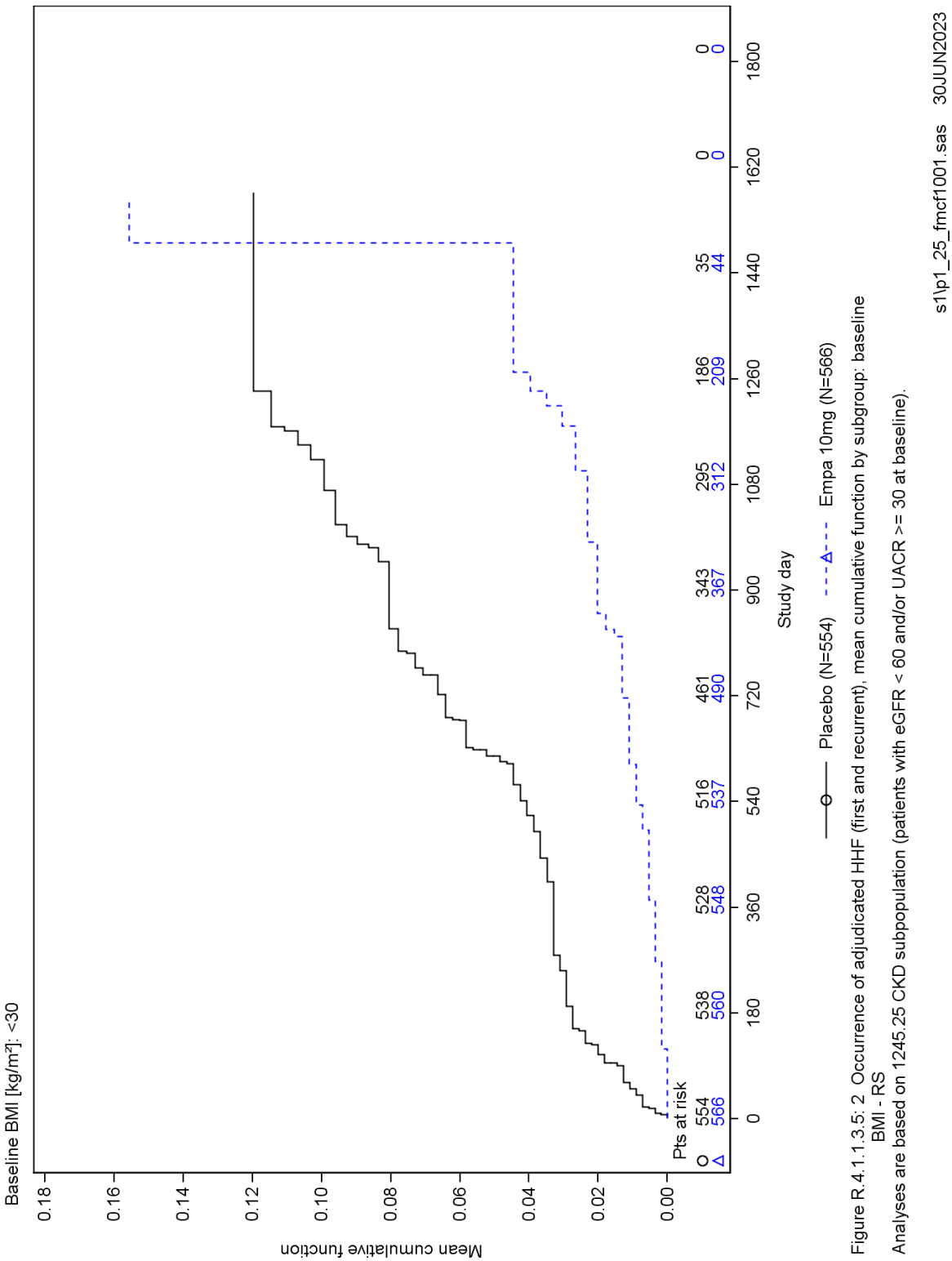


Figure R.4.1.1.3.5: 2 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: baseline BMI - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.5: 2**

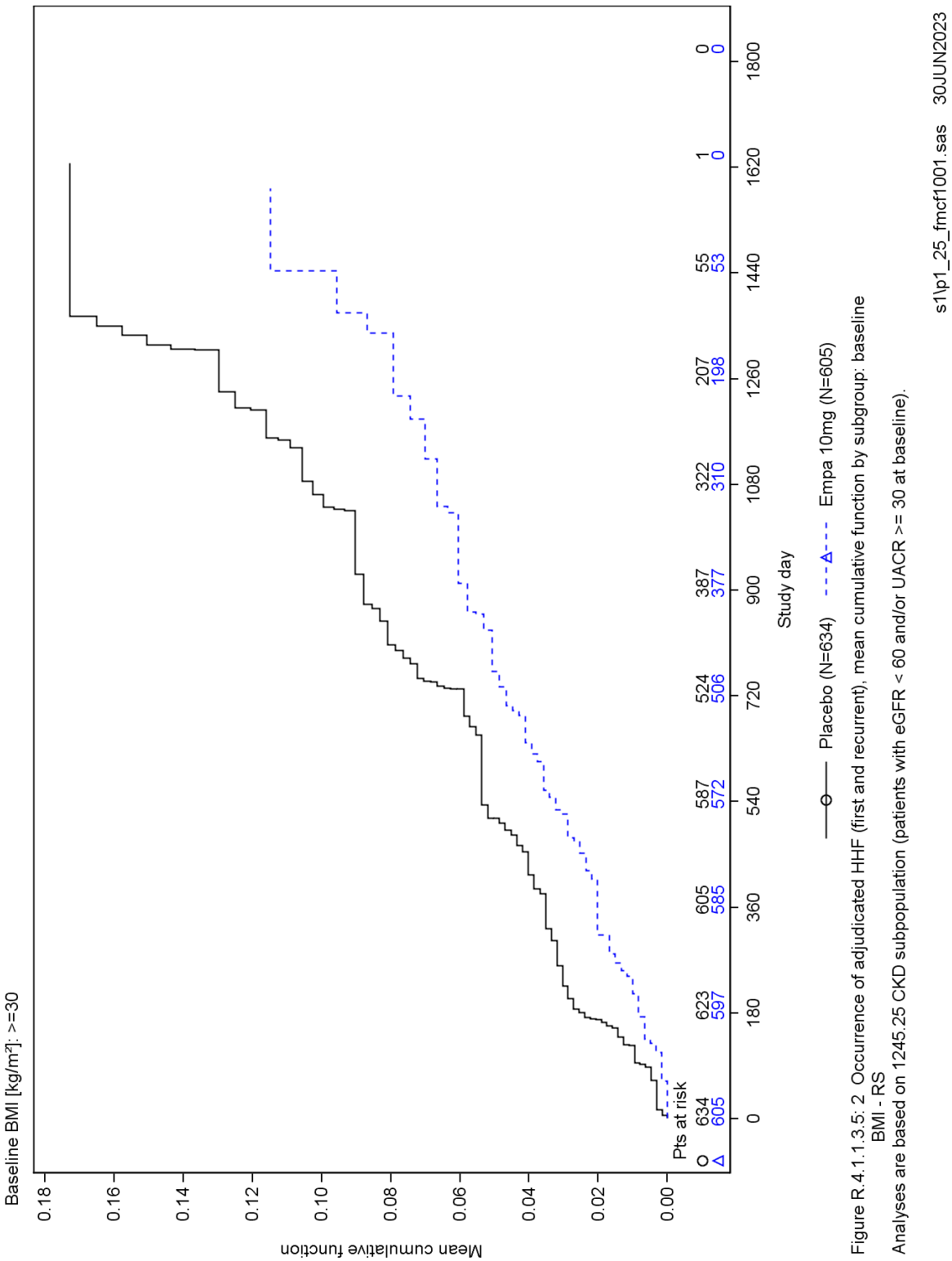


Figure R.4.1.1.3.5: 2 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: baseline BMI - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.4.1.1.3.6 Time to first occurrence of all-cause hospitalization

Table R.4.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1188 | 537 | 45.2 | 22.37 | 1171 | 471 | 40.2 | 18.34 | 0.83 | (0.73,0.94) | 0.0036 | |
| Sex | | | | | | | | | | | | 0.9630 |
| Male | 864 | 400 | 46.3 | 23.06 | 837 | 343 | 41.0 | 18.86 | 0.83 | (0.72,0.96) | 0.0134 | |
| Female | 324 | 137 | 42.3 | 20.58 | 334 | 128 | 38.3 | 17.08 | 0.83 | (0.65,1.05) | 0.1247 | |
| Age [years] | | | | | | | | | | | | 0.7983 |
| <65 | 569 | 240 | 42.2 | 19.80 | 547 | 207 | 37.8 | 16.38 | 0.84 | (0.70,1.02) | 0.0741 | |
| >=65 | 619 | 297 | 48.0 | 25.00 | 624 | 264 | 42.3 | 20.23 | 0.82 | (0.69,0.96) | 0.0170 | |
| Region | | | | | | | | | | | | 0.0944 |
| Europe | 468 | 219 | 46.8 | 23.64 | 434 | 182 | 41.9 | 19.73 | 0.85 | (0.70,1.04) | 0.1059 | |
| North America | 259 | 114 | 44.0 | 22.34 | 241 | 98 | 40.7 | 19.04 | 0.87 | (0.66,1.14) | 0.3134 | |
| Latin America | 177 | 79 | 44.6 | 22.18 | 191 | 65 | 34.0 | 15.01 | 0.66 | (0.48,0.92) | 0.0135 | |
| Africa | 50 | 29 | 58.0 | 32.27 | 54 | 20 | 37.0 | 15.83 | 0.48 | (0.27,0.84) | 0.0106 | |
| Asia | 234 | 96 | 41.0 | 18.55 | 251 | 106 | 42.2 | 18.53 | 1.03 | (0.78,1.35) | 0.8559 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5352 |
| <30 | 554 | 237 | 42.8 | 20.51 | 566 | 210 | 37.1 | 16.23 | 0.80 | (0.66,0.96) | 0.0163 | |
| >=30 | 634 | 300 | 47.3 | 24.10 | 605 | 261 | 43.1 | 20.48 | 0.86 | (0.73,1.02) | 0.0792 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5499 |
| <130 | 379 | 167 | 44.1 | 21.47 | 382 | 141 | 36.9 | 16.44 | 0.79 | (0.63,0.98) | 0.0353 | |
| >=130 | 809 | 370 | 45.7 | 22.81 | 789 | 330 | 41.8 | 19.29 | 0.85 | (0.74,0.99) | 0.0366 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7708 |
| <75 | 500 | 226 | 45.2 | 22.23 | 500 | 208 | 41.6 | 18.82 | 0.87 | (0.72,1.05) | 0.1336 | |
| 75 to <85 | 427 | 185 | 43.3 | 21.08 | 417 | 150 | 36.0 | 16.07 | 0.78 | (0.63,0.97) | 0.0242 | |
| >=85 | 261 | 126 | 48.3 | 24.90 | 254 | 113 | 44.5 | 21.32 | 0.84 | (0.65,1.09) | 0.1925 | |
| History of heart failure | | | | | | | | | | | | 0.0291 |
| No | 1048 | 454 | 43.3 | 20.78 | 1031 | 410 | 39.8 | 17.84 | 0.87 | (0.76,1.00) | 0.0481 | |
| Yes | 140 | 83 | 59.3 | 38.48 | 140 | 61 | 43.6 | 22.55 | 0.59 | (0.42,0.82) | 0.0016 | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.8259 |
| <45 | 179 | 94 | 52.5 | 28.13 | 178 | 82 | 46.1 | 22.88 | 0.81 | (0.60,1.09) | 0.1619 | |
| >=45 | 1009 | 443 | 43.9 | 21.44 | 993 | 389 | 39.2 | 17.60 | 0.84 | (0.73,0.96) | 0.0119 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.4.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.1368 |
| Normal (<30) | 250 | 117 | 46.8 | 23.02 | 257 | 93 | 36.2 | 15.50 | 0.69 | (0.52,0.90) | 0.0066 | |
| Microalbuminuria (30 to <=300) | 675 | 280 | 41.5 | 19.69 | 645 | 255 | 39.5 | 17.84 | 0.93 | (0.78,1.10) | 0.4025 | |
| Macroalbuminuria (>300) | 260 | 139 | 53.5 | 29.86 | 261 | 119 | 45.6 | 22.65 | 0.77 | (0.60,0.98) | 0.0364 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.8058 |
| Low, moderate or high | 1018 | 444 | 43.6 | 21.12 | 1001 | 384 | 38.4 | 17.04 | 0.83 | (0.72,0.95) | 0.0065 | |
| Very high | 167 | 92 | 55.1 | 31.31 | 162 | 83 | 51.2 | 27.54 | 0.86 | (0.64,1.16) | 0.3249 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5787 |
| No | 205 | 85 | 41.5 | 19.25 | 211 | 71 | 33.6 | 14.39 | 0.77 | (0.56,1.05) | 0.0990 | |
| Yes | 983 | 452 | 46.0 | 23.08 | 960 | 400 | 41.7 | 19.27 | 0.85 | (0.74,0.97) | 0.0144 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.1567 |
| No | 422 | 191 | 45.3 | 22.23 | 408 | 148 | 36.3 | 16.15 | 0.73 | (0.59,0.91) | 0.0046 | |
| Yes | 766 | 346 | 45.2 | 22.45 | 763 | 323 | 42.3 | 19.55 | 0.89 | (0.76,1.03) | 0.1197 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.7884 |
| No | 629 | 265 | 42.1 | 19.86 | 589 | 216 | 36.7 | 15.74 | 0.81 | (0.68,0.97) | 0.0244 | |
| Yes | 559 | 272 | 48.7 | 25.52 | 582 | 255 | 43.8 | 21.32 | 0.84 | (0.71,1.00) | 0.0481 | |

* Based on a Cox regression model with terms age, sex, baseline BMI, baseline HbA1c, baseline eGFR (CKD-EPI), region, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.6: 1**

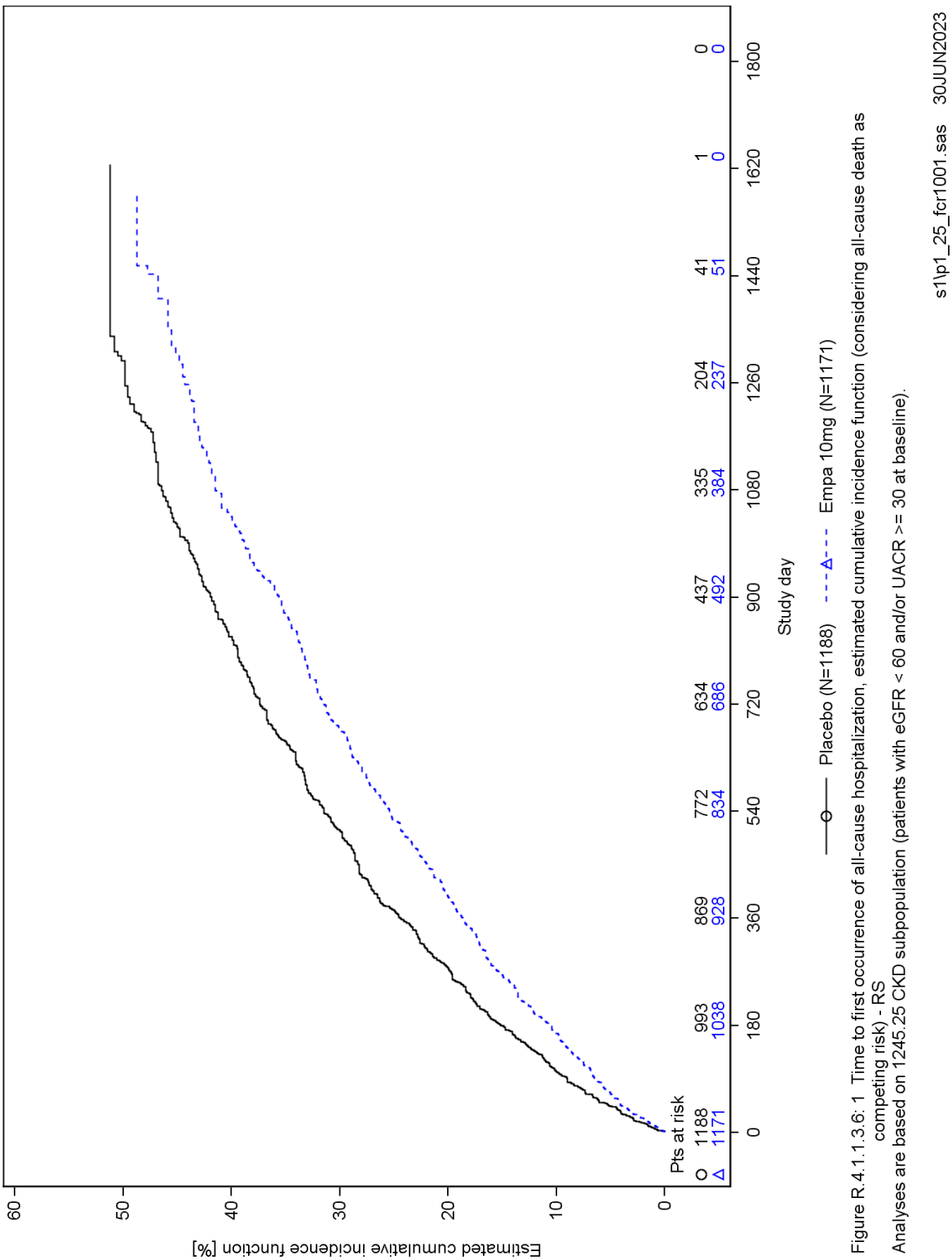


Figure R.4.1.1.3.6: 1 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.6: 2**

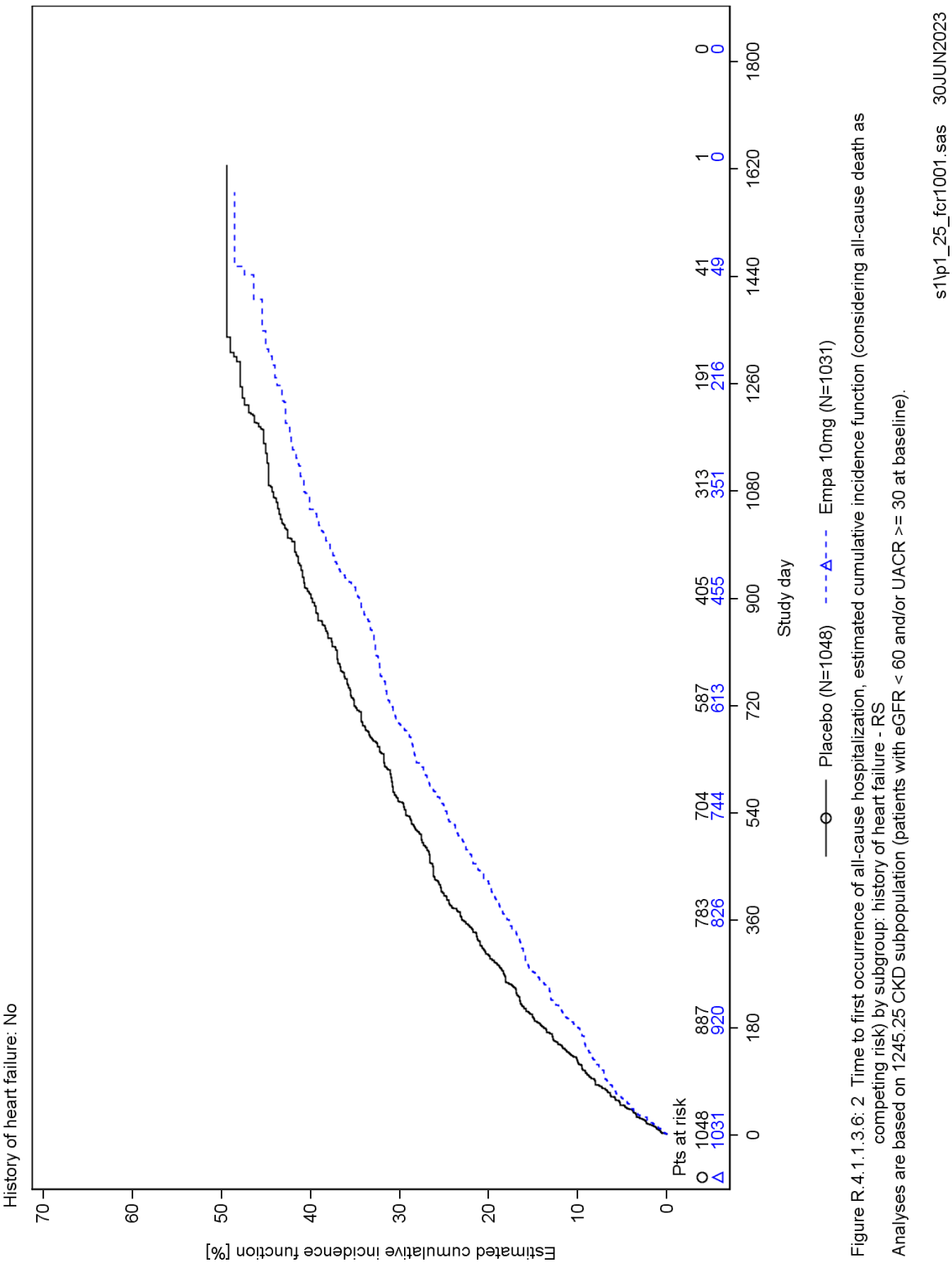


Figure R.4.1.1.3.6: 2 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: history of heart failure - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.6: 2**

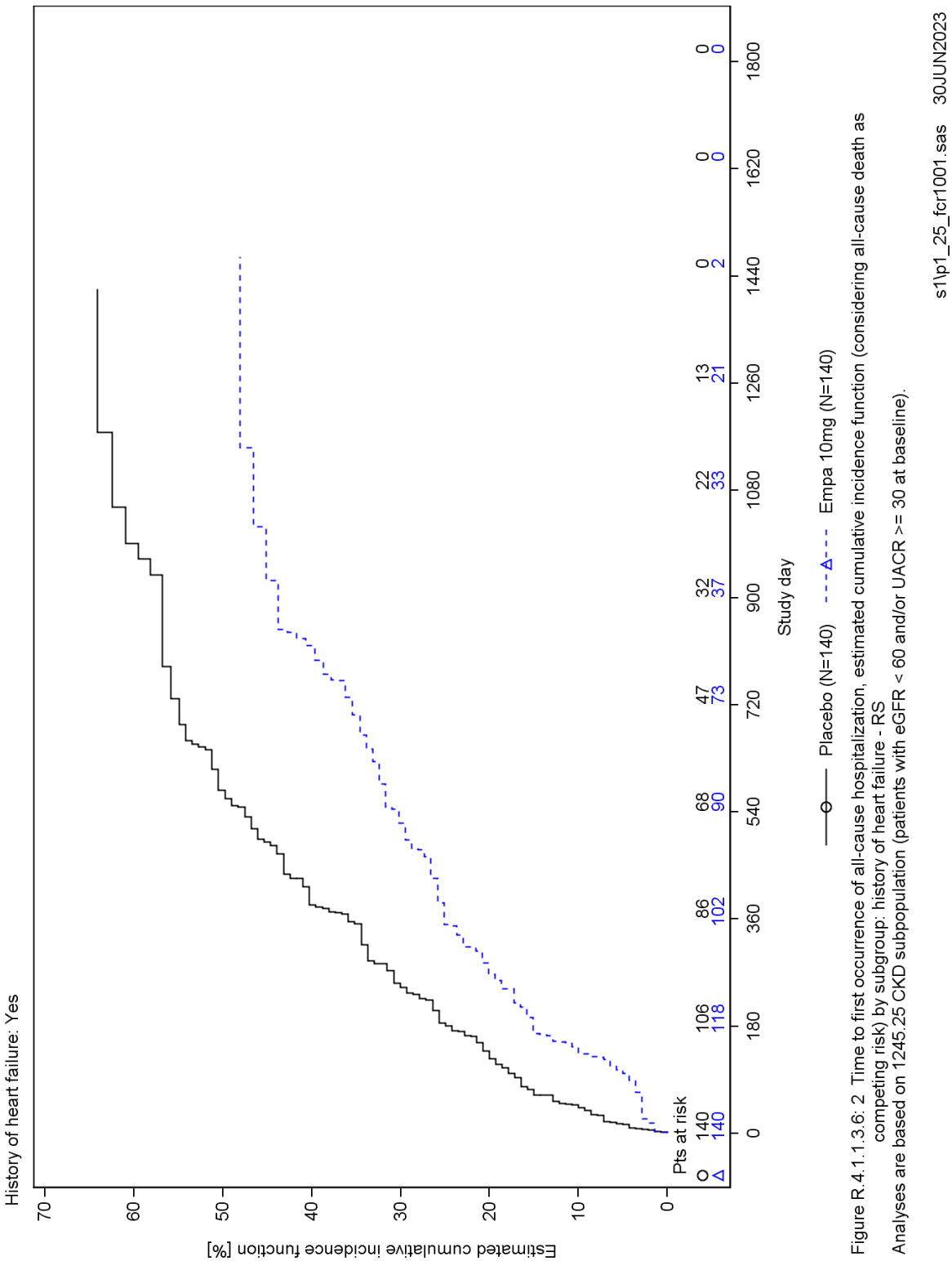


Figure R.4.1.1.3.6: 2 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: history of heart failure - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.4.1.1.3.7 Time to occurrence of all-cause hospitalizations (first and recurrent)

Table R.4.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 1188 | 537 | 45.2 | 1160 | 34.55 | 1171 | 471 | 40.2 | 909 | 26.96 | 0.75 | (0.66,0.87) | <0.0001 | |
| Sex | | | | | | | | | | | | | | 0.4710 |
| Male | 864 | 400 | 46.3 | 856 | 35.04 | 837 | 343 | 41.0 | 674 | 27.96 | 0.78 | (0.66,0.91) | 0.0022 | |
| Female | 324 | 137 | 42.3 | 304 | 33.24 | 334 | 128 | 38.3 | 235 | 24.44 | 0.69 | (0.53,0.90) | 0.0066 | |
| Age [years] | | | | | | | | | | | | | | 0.6043 |
| <65 | 569 | 240 | 42.2 | 476 | 29.29 | 547 | 207 | 37.8 | 386 | 23.78 | 0.78 | (0.64,0.96) | 0.0186 | |
| >=65 | 619 | 297 | 48.0 | 684 | 39.48 | 624 | 264 | 42.3 | 523 | 29.91 | 0.73 | (0.60,0.88) | 0.0008 | |
| Region | | | | | | | | | | | | | | 0.9777 |
| Europe | 468 | 219 | 46.8 | 534 | 40.08 | 434 | 182 | 41.9 | 370 | 30.06 | 0.77 | (0.62,0.96) | 0.0180 | |
| North America | 259 | 114 | 44.0 | 224 | 30.99 | 241 | 98 | 40.7 | 178 | 26.17 | 0.82 | (0.60,1.10) | 0.1837 | |
| Latin America | 177 | 79 | 44.6 | 131 | 27.02 | 191 | 65 | 34.0 | 115 | 21.21 | 0.71 | (0.49,1.03) | 0.0719 | |
| Africa | 50 | 29 | 58.0 | 57 | 39.95 | 54 | 20 | 37.0 | 47 | 30.86 | 0.72 | (0.38,1.35) | 0.3026 | |
| Asia | 234 | 96 | 41.0 | 214 | 31.70 | 251 | 106 | 42.2 | 199 | 25.96 | 0.73 | (0.54,0.98) | 0.0376 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1247 |
| <30 | 554 | 237 | 42.8 | 510 | 32.54 | 566 | 210 | 37.1 | 389 | 23.66 | 0.67 | (0.55,0.82) | 0.0001 | |
| >=30 | 634 | 300 | 47.3 | 650 | 36.31 | 605 | 261 | 43.1 | 520 | 30.10 | 0.83 | (0.69,1.00) | 0.0532 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2125 |
| <130 | 379 | 167 | 44.1 | 357 | 33.42 | 382 | 141 | 36.9 | 245 | 22.22 | 0.66 | (0.51,0.85) | 0.0011 | |
| >=130 | 809 | 370 | 45.7 | 803 | 35.08 | 789 | 330 | 41.8 | 664 | 29.26 | 0.80 | (0.68,0.94) | 0.0070 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7513 |
| <75 | 500 | 226 | 45.2 | 520 | 36.47 | 500 | 208 | 41.6 | 397 | 27.17 | 0.72 | (0.58,0.88) | 0.0018 | |
| 75 to <85 | 427 | 185 | 43.3 | 381 | 31.94 | 417 | 150 | 36.0 | 291 | 24.38 | 0.75 | (0.60,0.95) | 0.0182 | |
| >=85 | 261 | 126 | 48.3 | 259 | 35.06 | 254 | 113 | 44.5 | 221 | 30.81 | 0.82 | (0.62,1.10) | 0.1880 | |
| History of heart failure | | | | | | | | | | | | | | 0.0013 |
| No | 1048 | 454 | 43.3 | 894 | 29.93 | 1031 | 410 | 39.8 | 791 | 26.30 | 0.85 | (0.73,0.98) | 0.0271 | |
| Yes | 140 | 83 | 59.3 | 266 | 71.89 | 140 | 61 | 43.6 | 118 | 32.36 | 0.44 | (0.31,0.64) | <0.0001 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline BMI, baseline eGFR (CKD-EPI), baseline HbA1c, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.4.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8369 |
| <45 | 179 | 94 | 52.5 | 225 | 45.17 | 178 | 82 | 46.1 | 164 | 33.14 | 0.73 | (0.52,1.02) | 0.0663 | |
| >=45 | 1009 | 443 | 43.9 | 935 | 32.70 | 993 | 389 | 39.2 | 745 | 25.90 | 0.76 | (0.65,0.88) | 0.0003 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2018 |
| Normal (<30) | 250 | 117 | 46.8 | 252 | 34.37 | 257 | 93 | 36.2 | 176 | 23.39 | 0.69 | (0.52,0.93) | 0.0137 | |
| Microalbuminuria (30 to <=300) | 675 | 280 | 41.5 | 595 | 30.87 | 645 | 255 | 39.5 | 491 | 26.35 | 0.85 | (0.71,1.02) | 0.0817 | |
| Macroalbuminuria (>300) | 260 | 139 | 53.5 | 312 | 45.11 | 261 | 119 | 45.6 | 235 | 31.98 | 0.64 | (0.49,0.85) | 0.0019 | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8939 |
| Low, moderate or high | 1018 | 444 | 43.6 | 933 | 32.17 | 1001 | 384 | 38.4 | 727 | 24.97 | 0.76 | (0.65,0.88) | 0.0003 | |
| Very high | 167 | 92 | 55.1 | 226 | 49.98 | 162 | 83 | 51.2 | 175 | 39.90 | 0.74 | (0.52,1.04) | 0.0819 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.8108 |
| No | 205 | 85 | 41.5 | 166 | 28.30 | 211 | 71 | 33.6 | 147 | 23.58 | 0.73 | (0.52,1.02) | 0.0664 | |
| Yes | 983 | 452 | 46.0 | 994 | 35.87 | 960 | 400 | 41.7 | 762 | 27.72 | 0.76 | (0.66,0.88) | 0.0004 | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.0534 |
| No | 422 | 191 | 45.3 | 404 | 34.25 | 408 | 148 | 36.3 | 264 | 22.77 | 0.62 | (0.49,0.79) | <0.0001 | |
| Yes | 766 | 346 | 45.2 | 756 | 34.71 | 763 | 323 | 42.3 | 645 | 29.15 | 0.83 | (0.70,0.98) | 0.0296 | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.7302 |
| No | 629 | 265 | 42.1 | 480 | 26.90 | 589 | 216 | 36.7 | 375 | 21.66 | 0.77 | (0.63,0.94) | 0.0100 | |
| Yes | 559 | 272 | 48.7 | 680 | 43.23 | 582 | 255 | 43.8 | 534 | 32.54 | 0.73 | (0.61,0.88) | 0.0012 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline BMI, baseline eGFR (CKD-EPI), baseline HbA1c, subgroup, region, sex, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.7: 1**

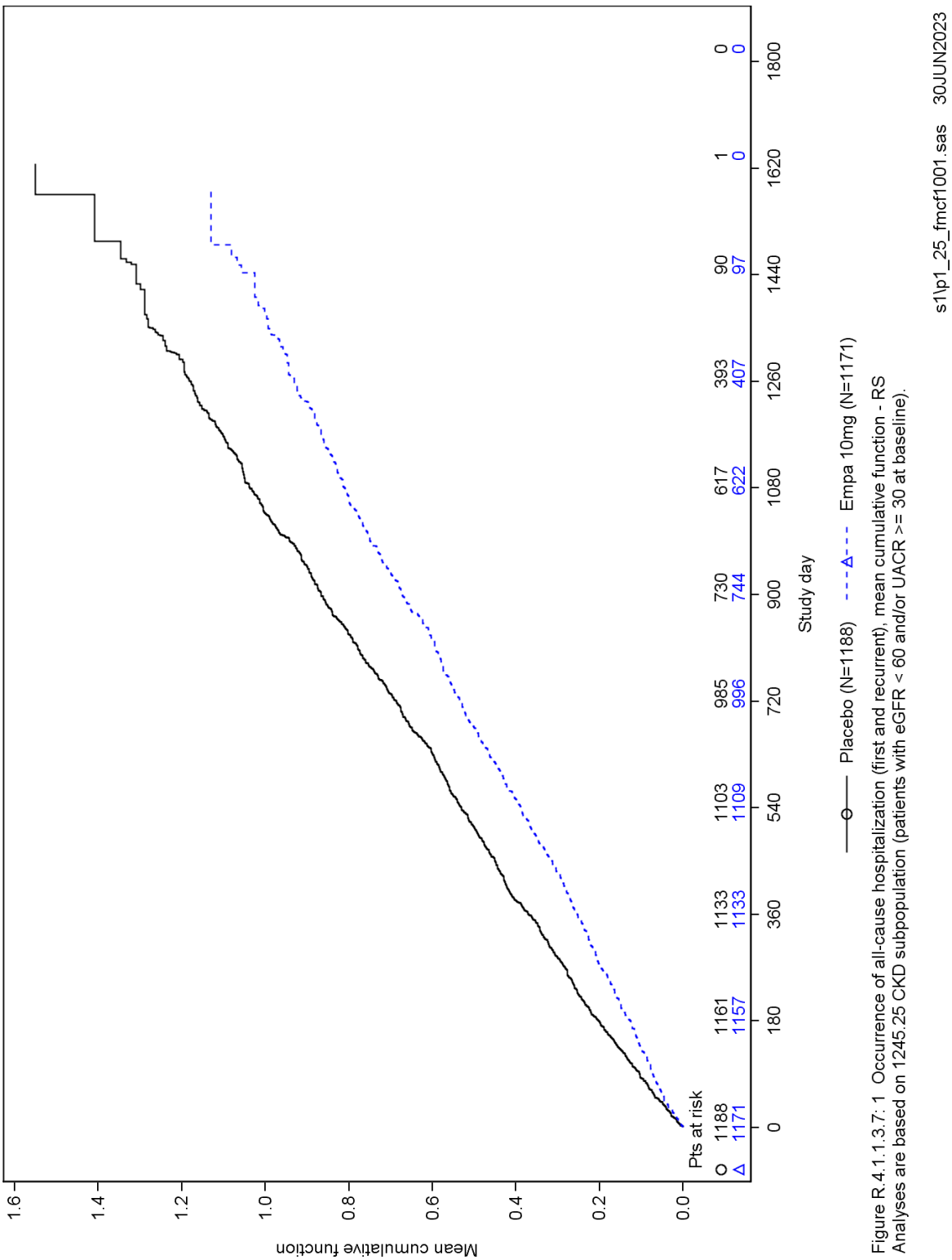


Figure R.4.1.1.3.7: 1 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function - RS
Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.7: 2**

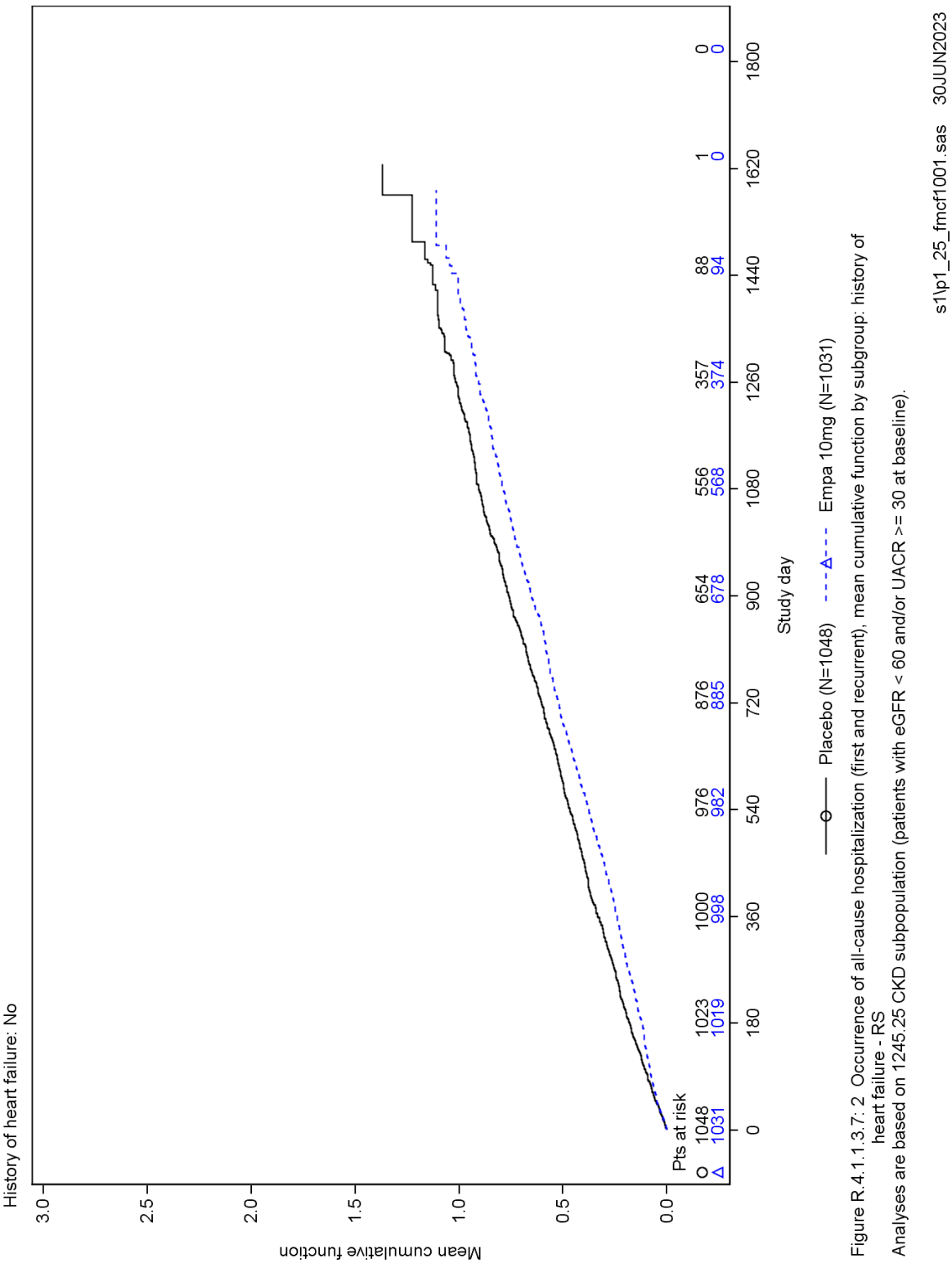


Figure R.4.1.1.3.7: 2 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: history of heart failure - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.4.1.1.3.7: 2**

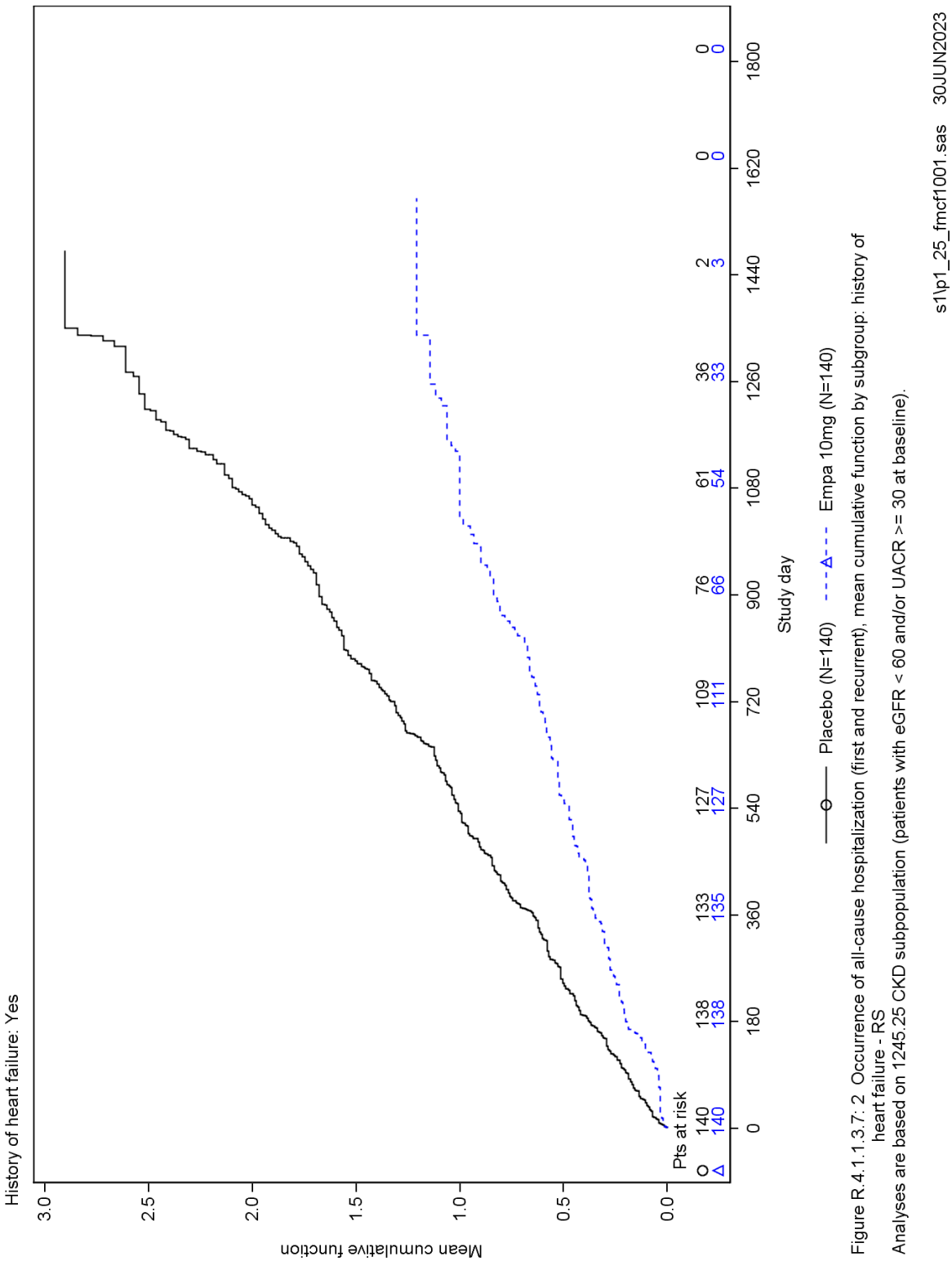


Figure R.4.1.1.3.7: 2 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: history of heart failure - RS

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.4.2**

**R.4.2.1**

R.4.2.1 Adverse events overall

Table R.4.2.1: 1 Proportion of patients with any adverse event occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 1121 | 94.4 | 1171 | 1093 | 93.3 | 0.3018 | 0.99 | (0.97, 1.01) | 0.84 | (0.60, 1.17) | -0.01 | (-0.03,0.01) | |
| Sex | | | | | | | | | | | | | | 0.0532 |
| Male | 864 | 819 | 94.8 | 837 | 775 | 92.6 | 0.0618 | 0.98 | (0.95,>1.00) | 0.69 | (0.46, 1.02) | -0.02 | (-0.05,0.00) | |
| Female | 324 | 302 | 93.2 | 334 | 318 | 95.2 | 0.2716 | 1.02 | (0.98, 1.06) | 1.45 | (0.75, 2.81) | 0.02 | (-0.02,0.06) | |
| Age [years] | | | | | | | | | | | | | | 0.1331 |
| <65 | 569 | 533 | 93.7 | 547 | 498 | 91.0 | 0.0976 | 0.97 | (0.94, 1.01) | 0.69 | (0.44, 1.07) | -0.03 | (-0.06,0.00) | |
| >=65 | 619 | 588 | 95.0 | 624 | 595 | 95.4 | 0.7668 | 1.00 | (0.98, 1.03) | 1.08 | (0.64, 1.82) | 0.00 | (-0.02,0.03) | |
| Region | | | | | | | | | | | | | | 0.4908 |
| Europe | 468 | 431 | 92.1 | 434 | 390 | 89.9 | 0.2413 | 0.98 | (0.94, 1.02) | 0.76 | (0.48, 1.20) | -0.02 | (-0.06,0.02) | |
| North America | 259 | 244 | 94.2 | 241 | 230 | 95.4 | 0.5369 | 1.01 | (0.97, 1.06) | 1.29 | (0.58, 2.86) | 0.01 | (-0.03,0.05) | |
| Latin America | 177 | 169 | 95.5 | 191 | 181 | 94.8 | 0.7504 | 0.99 | (0.95, 1.04) | 0.86 | (0.33, 2.22) | -0.01 | (-0.05,0.04) | |
| Africa | 50 | 47 | 94.0 | 54 | 52 | 96.3 | 0.5844 | 1.02 | (0.94, 1.12) | 1.66 | (0.27,10.37) | 0.02 | (-0.06,0.11) | |
| Asia | 234 | 230 | 98.3 | 251 | 240 | 95.6 | 0.0893 | 0.97 | (0.94,>1.00) | 0.38 | (0.12, 1.21) | -0.03 | (-0.06,0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4380 |
| <30 | 554 | 523 | 94.4 | 566 | 533 | 94.2 | 0.8656 | 1.00 | (0.97, 1.03) | 0.96 | (0.58, 1.59) | 0.00 | (-0.03,0.02) | |
| >=30 | 634 | 598 | 94.3 | 605 | 560 | 92.6 | 0.2103 | 0.98 | (0.95, 1.01) | 0.75 | (0.48, 1.18) | -0.02 | (-0.05,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2833 |
| <130 | 379 | 359 | 94.7 | 382 | 352 | 92.1 | 0.1515 | 0.97 | (0.94, 1.01) | 0.65 | (0.36, 1.17) | -0.03 | (-0.06,0.01) | |
| >=130 | 809 | 762 | 94.2 | 789 | 741 | 93.9 | 0.8169 | 1.00 | (0.97, 1.02) | 0.95 | (0.63, 1.44) | 0.00 | (-0.03,0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5475 |
| <75 | 500 | 478 | 95.6 | 500 | 468 | 93.6 | 0.1618 | 0.98 | (0.95, 1.01) | 0.67 | (0.39, 1.18) | -0.02 | (-0.05,0.01) | |
| 75 to <85 | 427 | 402 | 94.1 | 417 | 388 | 93.0 | 0.5140 | 0.99 | (0.95, 1.02) | 0.83 | (0.48, 1.45) | -0.01 | (-0.04,0.02) | |
| >=85 | 261 | 241 | 92.3 | 254 | 237 | 93.3 | 0.6700 | 1.01 | (0.96, 1.06) | 1.16 | (0.59, 2.26) | 0.01 | (-0.03,0.05) | |
| History of heart failure | | | | | | | | | | | | | | 0.3206 |
| No | 1048 | 986 | 94.1 | 1031 | 963 | 93.4 | 0.5223 | 0.99 | (0.97, 1.02) | 0.89 | (0.62, 1.27) | -0.01 | (-0.03,0.01) | |
| Yes | 140 | 135 | 96.4 | 140 | 130 | 92.9 | 0.1845 | 0.96 | (0.91, 1.02) | 0.48 | (0.16, 1.45) | -0.04 | (-0.09,0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 1 Proportion of patients with any adverse event occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2802 |
| <45 | 179 | 173 | 96.6 | 178 | 166 | 93.3 | 0.1433 | 0.96 | (0.92, 1.01) | 0.48 | (0.18, 1.31) | -0.03 | (-0.08,0.01) | |
| >=45 | 1009 | 948 | 94.0 | 993 | 927 | 93.4 | 0.5813 | 0.99 | (0.97, 1.02) | 0.90 | (0.63, 1.29) | -0.01 | (-0.03,0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6435 |
| Normal (<30) | 250 | 239 | 95.6 | 257 | 239 | 93.0 | 0.2069 | 0.97 | (0.93, 1.02) | 0.61 | (0.28, 1.32) | -0.03 | (-0.07,0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 633 | 93.8 | 645 | 598 | 92.7 | 0.4407 | 0.99 | (0.96, 1.02) | 0.84 | (0.55, 1.30) | -0.01 | (-0.04,0.02) | |
| Macroalbuminuria (>300) | 260 | 247 | 95.0 | 261 | 248 | 95.0 | 0.9920 | 1.00 | (0.96, 1.04) | 1.00 | (0.46, 2.21) | 0.00 | (-0.04,0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4863 |
| Low, moderate or high | 1018 | 961 | 94.4 | 1001 | 931 | 93.0 | 0.1971 | 0.99 | (0.96, 1.01) | 0.79 | (0.55, 1.13) | -0.01 | (-0.04,0.01) | |
| Very high | 167 | 158 | 94.6 | 162 | 154 | 95.1 | 0.8534 | 1.00 | (0.96, 1.06) | 1.10 | (0.41, 2.92) | 0.00 | (-0.04,0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7220 |
| No | 205 | 195 | 95.1 | 211 | 200 | 94.8 | 0.8759 | 1.00 | (0.95, 1.04) | 0.93 | (0.39, 2.25) | 0.00 | (-0.05,0.04) | |
| Yes | 983 | 926 | 94.2 | 960 | 893 | 93.0 | 0.2871 | 0.99 | (0.96, 1.01) | 0.82 | (0.57, 1.18) | -0.01 | (-0.03,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8081 |
| No | 422 | 397 | 94.1 | 408 | 381 | 93.4 | 0.6802 | 0.99 | (0.96, 1.03) | 0.89 | (0.51, 1.56) | -0.01 | (-0.04,0.03) | |
| Yes | 766 | 724 | 94.5 | 763 | 712 | 93.3 | 0.3258 | 0.99 | (0.96, 1.01) | 0.81 | (0.53, 1.23) | -0.01 | (-0.04,0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3280 |
| No | 629 | 587 | 93.3 | 589 | 549 | 93.2 | 0.9368 | 1.00 | (0.97, 1.03) | 0.98 | (0.63, 1.54) | 0.00 | (-0.03,0.03) | |
| Yes | 559 | 534 | 95.5 | 582 | 544 | 93.5 | 0.1283 | 0.98 | (0.95, 1.01) | 0.67 | (0.40, 1.13) | -0.02 | (-0.05,0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 1107 | 93.2 | 1171 | 1063 | 90.8 | 0.0315 | 0.97 | (0.95,<1.00) | 0.72 | (0.53, 0.97) | -0.02 | (-0.05, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0168 |
| Male | 864 | 809 | 93.6 | 837 | 750 | 89.6 | 0.0027 | 0.96 | (0.93, 0.99) | 0.59 | (0.41, 0.83) | -0.04 | (-0.07,-0.01) | |
| Female | 324 | 298 | 92.0 | 334 | 313 | 93.7 | 0.3870 | 1.02 | (0.98, 1.06) | 1.30 | (0.72, 2.36) | 0.02 | (-0.02, 0.06) | |
| Age [years] | | | | | | | | | | | | | | 0.0791 |
| <65 | 569 | 527 | 92.6 | 547 | 482 | 88.1 | 0.0107 | 0.95 | (0.92, 0.99) | 0.59 | (0.39, 0.89) | -0.05 | (-0.08,-0.01) | |
| >=65 | 619 | 580 | 93.7 | 624 | 581 | 93.1 | 0.6749 | 0.99 | (0.96, 1.02) | 0.91 | (0.58, 1.42) | -0.01 | (-0.03, 0.02) | |
| Region | | | | | | | | | | | | | | 0.6699 |
| Europe | 468 | 420 | 89.7 | 434 | 375 | 86.4 | 0.1213 | 0.96 | (0.92, 1.01) | 0.73 | (0.48, 1.09) | -0.03 | (-0.08, 0.01) | |
| North America | 259 | 243 | 93.8 | 241 | 224 | 92.9 | 0.6933 | 0.99 | (0.95, 1.04) | 0.87 | (0.43, 1.76) | -0.01 | (-0.05, 0.03) | |
| Latin America | 177 | 168 | 94.9 | 191 | 174 | 91.1 | 0.1535 | 0.96 | (0.91, 1.02) | 0.55 | (0.24, 1.26) | -0.04 | (-0.09, 0.01) | |
| Africa | 50 | 47 | 94.0 | 54 | 52 | 96.3 | 0.5844 | 1.02 | (0.94, 1.12) | 1.66 | (0.27,10.37) | 0.02 | (-0.06, 0.11) | |
| Asia | 234 | 229 | 97.9 | 251 | 238 | 94.8 | 0.0765 | 0.97 | (0.94,>1.00) | 0.40 | (0.14, 1.14) | -0.03 | (-0.06, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8126 |
| <30 | 554 | 519 | 93.7 | 566 | 518 | 91.5 | 0.1671 | 0.98 | (0.95, 1.01) | 0.73 | (0.46, 1.14) | -0.02 | (-0.05, 0.01) | |
| >=30 | 634 | 588 | 92.7 | 605 | 545 | 90.1 | 0.0940 | 0.97 | (0.94, 1.01) | 0.71 | (0.48, 1.06) | -0.03 | (-0.06, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2216 |
| <130 | 379 | 355 | 93.7 | 382 | 341 | 89.3 | 0.0299 | 0.95 | (0.91,<1.00) | 0.56 | (0.33, 0.95) | -0.04 | (-0.08, 0.00) | |
| >=130 | 809 | 752 | 93.0 | 789 | 722 | 91.5 | 0.2800 | 0.98 | (0.96, 1.01) | 0.82 | (0.57, 1.18) | -0.01 | (-0.04, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8279 |
| <75 | 500 | 473 | 94.6 | 500 | 460 | 92.0 | 0.1001 | 0.97 | (0.94, 1.01) | 0.66 | (0.40, 1.09) | -0.03 | (-0.06, 0.00) | |
| 75 to <85 | 427 | 397 | 93.0 | 417 | 375 | 89.9 | 0.1132 | 0.97 | (0.93, 1.01) | 0.67 | (0.41, 1.10) | -0.03 | (-0.07, 0.01) | |
| >=85 | 261 | 237 | 90.8 | 254 | 228 | 89.8 | 0.6900 | 0.99 | (0.93, 1.05) | 0.89 | (0.50, 1.59) | -0.01 | (-0.06, 0.04) | |
| History of heart failure | | | | | | | | | | | | | | 0.5539 |
| No | 1048 | 977 | 93.2 | 1031 | 939 | 91.1 | 0.0684 | 0.98 | (0.95,>1.00) | 0.74 | (0.54, 1.02) | -0.02 | (-0.04, 0.00) | |
| Yes | 140 | 130 | 92.9 | 140 | 124 | 88.6 | 0.2167 | 0.95 | (0.88, 1.03) | 0.60 | (0.26, 1.36) | -0.04 | (-0.11, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related events are defined as all events from the SOC `Cardiac Disorders´ and the SOC `Renal and urinary disorders´.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3936 |
| <45 | 179 | 172 | 96.1 | 178 | 163 | 91.6 | 0.0760 | 0.95 | (0.90, 1.01) | 0.44 | (0.18, 1.11) | -0.05 | (-0.09, 0.00) | |
| >=45 | 1009 | 935 | 92.7 | 993 | 900 | 90.6 | 0.1003 | 0.98 | (0.95,>1.00) | 0.77 | (0.56, 1.05) | -0.02 | (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4721 |
| Normal (<30) | 250 | 236 | 94.4 | 257 | 230 | 89.5 | 0.0428 | 0.95 | (0.90,<1.00) | 0.51 | (0.26, 0.99) | -0.05 | (-0.10, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 623 | 92.3 | 645 | 586 | 90.9 | 0.3448 | 0.98 | (0.95, 1.02) | 0.83 | (0.56, 1.22) | -0.01 | (-0.04, 0.02) | |
| Macroalbuminuria (>300) | 260 | 246 | 94.6 | 261 | 239 | 91.6 | 0.1707 | 0.97 | (0.92, 1.01) | 0.62 | (0.31, 1.24) | -0.03 | (-0.07, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8270 |
| Low, moderate or high | 1018 | 947 | 93.0 | 1001 | 905 | 90.4 | 0.0329 | 0.97 | (0.95,<1.00) | 0.71 | (0.51, 0.97) | -0.03 | (-0.05, 0.00) | |
| Very high | 167 | 158 | 94.6 | 162 | 150 | 92.6 | 0.4541 | 0.98 | (0.92, 1.04) | 0.71 | (0.29, 1.74) | -0.02 | (-0.07, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9168 |
| No | 205 | 193 | 94.1 | 211 | 193 | 91.5 | 0.2913 | 0.97 | (0.92, 1.02) | 0.67 | (0.31, 1.42) | -0.03 | (-0.08, 0.02) | |
| Yes | 983 | 914 | 93.0 | 960 | 870 | 90.6 | 0.0582 | 0.97 | (0.95,>1.00) | 0.73 | (0.53, 1.01) | -0.02 | (-0.05, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8573 |
| No | 422 | 394 | 93.4 | 408 | 370 | 90.7 | 0.1539 | 0.97 | (0.93, 1.01) | 0.69 | (0.42, 1.15) | -0.03 | (-0.06, 0.01) | |
| Yes | 766 | 713 | 93.1 | 763 | 693 | 90.8 | 0.1050 | 0.98 | (0.95, 1.01) | 0.74 | (0.51, 1.07) | -0.02 | (-0.05, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5006 |
| No | 629 | 584 | 92.8 | 589 | 537 | 91.2 | 0.2808 | 0.98 | (0.95, 1.02) | 0.80 | (0.52, 1.21) | -0.02 | (-0.05, 0.01) | |
| Yes | 559 | 523 | 93.6 | 582 | 526 | 90.4 | 0.0484 | 0.97 | (0.93,<1.00) | 0.65 | (0.42, 1.00) | -0.03 | (-0.06, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related events are defined as all events from the SOC `Cardiac Disorders´ and the SOC `Renal and urinary disorders´.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 3 Proportion of patients with serious adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 627 | 52.8 | 1171 | 543 | 46.4 | 0.0019 | 0.88 | (0.81, 0.95) | 0.77 | (0.66,0.91) | -0.06 | (-0.10,-0.02) | |
| Sex | | | | | | | | | | | | | | 0.7262 |
| Male | 864 | 470 | 54.4 | 837 | 397 | 47.4 | 0.0041 | 0.87 | (0.79, 0.96) | 0.76 | (0.63,0.92) | -0.07 | (-0.12,-0.02) | |
| Female | 324 | 157 | 48.5 | 334 | 146 | 43.7 | 0.2222 | 0.90 | (0.76, 1.06) | 0.83 | (0.61,1.12) | -0.05 | (-0.12, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.6012 |
| <65 | 569 | 273 | 48.0 | 547 | 236 | 43.1 | 0.1050 | 0.90 | (0.79, 1.02) | 0.82 | (0.65,1.04) | -0.05 | (-0.11, 0.01) | |
| >=65 | 619 | 354 | 57.2 | 624 | 307 | 49.2 | 0.0048 | 0.86 | (0.77, 0.96) | 0.72 | (0.58,0.91) | -0.08 | (-0.14,-0.02) | |
| Region | | | | | | | | | | | | | | 0.2871 |
| Europe | 468 | 250 | 53.4 | 434 | 210 | 48.4 | 0.1309 | 0.91 | (0.80, 1.03) | 0.82 | (0.63,1.06) | -0.05 | (-0.12, 0.01) | |
| North America | 259 | 134 | 51.7 | 241 | 119 | 49.4 | 0.5979 | 0.95 | (0.80, 1.14) | 0.91 | (0.64,1.29) | -0.02 | (-0.11, 0.06) | |
| Latin America | 177 | 96 | 54.2 | 191 | 76 | 39.8 | 0.0055 | 0.73 | (0.59, 0.91) | 0.56 | (0.37,0.84) | -0.14 | (-0.25,-0.04) | |
| Africa | 50 | 31 | 62.0 | 54 | 24 | 44.4 | 0.0731 | 0.72 | (0.50, 1.04) | 0.49 | (0.22,1.07) | -0.18 | (-0.36, 0.01) | |
| Asia | 234 | 116 | 49.6 | 251 | 114 | 45.4 | 0.3599 | 0.92 | (0.76, 1.10) | 0.85 | (0.59,1.21) | -0.04 | (-0.13, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3308 |
| <30 | 554 | 285 | 51.4 | 566 | 245 | 43.3 | 0.0063 | 0.84 | (0.74, 0.95) | 0.72 | (0.57,0.91) | -0.08 | (-0.14,-0.02) | |
| >=30 | 634 | 342 | 53.9 | 605 | 298 | 49.3 | 0.0989 | 0.91 | (0.82, 1.02) | 0.83 | (0.66,1.04) | -0.05 | (-0.10, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7978 |
| <130 | 379 | 195 | 51.5 | 382 | 170 | 44.5 | 0.0551 | 0.86 | (0.75,>1.00) | 0.76 | (0.57,1.01) | -0.07 | (-0.14, 0.00) | |
| >=130 | 809 | 432 | 53.4 | 789 | 373 | 47.3 | 0.0144 | 0.89 | (0.80, 0.98) | 0.78 | (0.64,0.95) | -0.06 | (-0.11,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2380 |
| <75 | 500 | 268 | 53.6 | 500 | 249 | 49.8 | 0.2292 | 0.93 | (0.82, 1.05) | 0.86 | (0.67,1.10) | -0.04 | (-0.10, 0.02) | |
| 75 to <85 | 427 | 216 | 50.6 | 417 | 167 | 40.0 | 0.0021 | 0.79 | (0.68, 0.92) | 0.65 | (0.50,0.86) | -0.11 | (-0.17,-0.04) | |
| >=85 | 261 | 143 | 54.8 | 254 | 127 | 50.0 | 0.2766 | 0.91 | (0.77, 1.08) | 0.83 | (0.58,1.17) | -0.05 | (-0.13, 0.04) | |
| History of heart failure | | | | | | | | | | | | | | 0.3015 |
| No | 1048 | 533 | 50.9 | 1031 | 468 | 45.4 | 0.0126 | 0.89 | (0.82, 0.98) | 0.80 | (0.68,0.95) | -0.05 | (-0.10,-0.01) | |
| Yes | 140 | 94 | 67.1 | 140 | 75 | 53.6 | 0.0203 | 0.80 | (0.66, 0.97) | 0.56 | (0.35,0.92) | -0.14 | (-0.25,-0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 3 Proportion of patients with serious adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7298 |
| <45 | 179 | 109 | 60.9 | 178 | 98 | 55.1 | 0.2639 | 0.90 | (0.76, 1.08) | 0.79 | (0.52,1.20) | -0.06 | (-0.16, 0.04) | |
| >=45 | 1009 | 518 | 51.3 | 993 | 445 | 44.8 | 0.0035 | 0.87 | (0.80, 0.96) | 0.77 | (0.65,0.92) | -0.07 | (-0.11,-0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6798 |
| Normal (<30) | 250 | 139 | 55.6 | 257 | 118 | 45.9 | 0.0292 | 0.83 | (0.69, 0.98) | 0.68 | (0.48,0.96) | -0.10 | (-0.18,-0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 324 | 48.0 | 645 | 280 | 43.4 | 0.0943 | 0.90 | (0.80, 1.02) | 0.83 | (0.67,1.03) | -0.05 | (-0.10, 0.01) | |
| Macroalbuminuria (>300) | 260 | 163 | 62.7 | 261 | 141 | 54.0 | 0.0448 | 0.86 | (0.74,<1.00) | 0.70 | (0.49,0.99) | -0.09 | (-0.17, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3003 |
| Low, moderate or high | 1018 | 519 | 51.0 | 1001 | 440 | 44.0 | 0.0016 | 0.86 | (0.79, 0.95) | 0.75 | (0.63,0.90) | -0.07 | (-0.11,-0.03) | |
| Very high | 167 | 107 | 64.1 | 162 | 99 | 61.1 | 0.5790 | 0.95 | (0.81, 1.13) | 0.88 | (0.56,1.38) | -0.03 | (-0.13, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2025 |
| No | 205 | 103 | 50.2 | 211 | 82 | 38.9 | 0.0195 | 0.77 | (0.62, 0.96) | 0.63 | (0.43,0.93) | -0.11 | (-0.21,-0.02) | |
| Yes | 983 | 524 | 53.3 | 960 | 461 | 48.0 | 0.0198 | 0.90 | (0.82, 0.98) | 0.81 | (0.68,0.97) | -0.05 | (-0.10,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.0519 |
| No | 422 | 219 | 51.9 | 408 | 165 | 40.4 | 0.0009 | 0.78 | (0.67, 0.90) | 0.63 | (0.48,0.83) | -0.11 | (-0.18,-0.05) | |
| Yes | 766 | 408 | 53.3 | 763 | 378 | 49.5 | 0.1454 | 0.93 | (0.84, 1.03) | 0.86 | (0.70,1.05) | -0.04 | (-0.09, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8628 |
| No | 629 | 296 | 47.1 | 589 | 244 | 41.4 | 0.0480 | 0.88 | (0.78,<1.00) | 0.80 | (0.63,1.00) | -0.06 | (-0.11, 0.00) | |
| Yes | 559 | 331 | 59.2 | 582 | 299 | 51.4 | 0.0078 | 0.87 | (0.78, 0.96) | 0.73 | (0.58,0.92) | -0.08 | (-0.14,-0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 504 | 42.4 | 1171 | 451 | 38.5 | 0.0531 | 0.91 | (0.82,>1.00) | 0.85 | (0.72,1.00) | -0.04 | (-0.08, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.7466 |
| Male | 864 | 373 | 43.2 | 837 | 325 | 38.8 | 0.0687 | 0.90 | (0.80, 1.01) | 0.84 | (0.69,1.01) | -0.04 | (-0.09, 0.00) | |
| Female | 324 | 131 | 40.4 | 334 | 126 | 37.7 | 0.4767 | 0.93 | (0.77, 1.13) | 0.89 | (0.65,1.22) | -0.03 | (-0.10, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.5751 |
| <65 | 569 | 223 | 39.2 | 547 | 188 | 34.4 | 0.0950 | 0.88 | (0.75, 1.02) | 0.81 | (0.64,1.04) | -0.05 | (-0.10, 0.01) | |
| >=65 | 619 | 281 | 45.4 | 624 | 263 | 42.1 | 0.2484 | 0.93 | (0.82, 1.05) | 0.88 | (0.70,1.10) | -0.03 | (-0.09, 0.02) | |
| Region | | | | | | | | | | | | | | 0.3632 |
| Europe | 468 | 194 | 41.5 | 434 | 167 | 38.5 | 0.3624 | 0.93 | (0.79, 1.09) | 0.88 | (0.68,1.15) | -0.03 | (-0.09, 0.03) | |
| North America | 259 | 112 | 43.2 | 241 | 105 | 43.6 | 0.9416 | 1.01 | (0.82, 1.23) | 1.01 | (0.71,1.44) | 0.00 | (-0.08, 0.09) | |
| Latin America | 177 | 74 | 41.8 | 191 | 57 | 29.8 | 0.0166 | 0.71 | (0.54, 0.94) | 0.59 | (0.38,0.91) | -0.12 | (-0.22,-0.02) | |
| Africa | 50 | 25 | 50.0 | 54 | 22 | 40.7 | 0.3432 | 0.81 | (0.53, 1.25) | 0.69 | (0.32,1.49) | -0.09 | (-0.28, 0.10) | |
| Asia | 234 | 99 | 42.3 | 251 | 100 | 39.8 | 0.5810 | 0.94 | (0.76, 1.17) | 0.90 | (0.63,1.30) | -0.02 | (-0.11, 0.06) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6988 |
| <30 | 554 | 231 | 41.7 | 566 | 210 | 37.1 | 0.1156 | 0.89 | (0.77, 1.03) | 0.82 | (0.65,1.05) | -0.05 | (-0.10, 0.01) | |
| >=30 | 634 | 273 | 43.1 | 605 | 241 | 39.8 | 0.2494 | 0.93 | (0.81, 1.06) | 0.88 | (0.70,1.10) | -0.03 | (-0.09, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4280 |
| <130 | 379 | 147 | 38.8 | 382 | 143 | 37.4 | 0.7010 | 0.97 | (0.81, 1.16) | 0.94 | (0.70,1.27) | -0.01 | (-0.08, 0.06) | |
| >=130 | 809 | 357 | 44.1 | 789 | 308 | 39.0 | 0.0390 | 0.88 | (0.79, 0.99) | 0.81 | (0.66,0.99) | -0.05 | (-0.10, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4396 |
| <75 | 500 | 215 | 43.0 | 500 | 207 | 41.4 | 0.6085 | 0.96 | (0.83, 1.11) | 0.94 | (0.73,1.20) | -0.02 | (-0.08, 0.05) | |
| 75 to <85 | 427 | 174 | 40.7 | 417 | 141 | 33.8 | 0.0372 | 0.83 | (0.70, 0.99) | 0.74 | (0.56,0.98) | -0.07 | (-0.13, 0.00) | |
| >=85 | 261 | 115 | 44.1 | 254 | 103 | 40.6 | 0.4202 | 0.92 | (0.75, 1.13) | 0.87 | (0.61,1.23) | -0.04 | (-0.12, 0.05) | |
| History of heart failure | | | | | | | | | | | | | | 0.1761 |
| No | 1048 | 430 | 41.0 | 1031 | 394 | 38.2 | 0.1895 | 0.93 | (0.84, 1.04) | 0.89 | (0.75,1.06) | -0.03 | (-0.07, 0.01) | |
| Yes | 140 | 74 | 52.9 | 140 | 57 | 40.7 | 0.0417 | 0.77 | (0.60, 0.99) | 0.61 | (0.38,0.98) | -0.12 | (-0.24,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related events are defined as all events from the SOC `Cardiac Disorders´ and the SOC `Renal and urinary disorders´.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6729 |
| <45 | 179 | 87 | 48.6 | 178 | 82 | 46.1 | 0.6313 | 0.95 | (0.76, 1.18) | 0.90 | (0.60,1.37) | -0.03 | (-0.13, 0.08) | |
| >=45 | 1009 | 417 | 41.3 | 993 | 369 | 37.2 | 0.0562 | 0.90 | (0.81,>1.00) | 0.84 | (0.70,1.00) | -0.04 | (-0.08, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2420 |
| Normal (<30) | 250 | 112 | 44.8 | 257 | 94 | 36.6 | 0.0594 | 0.82 | (0.66, 1.01) | 0.71 | (0.50,1.01) | -0.08 | (-0.17, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 252 | 37.3 | 645 | 236 | 36.6 | 0.7795 | 0.98 | (0.85, 1.13) | 0.97 | (0.77,1.21) | -0.01 | (-0.06, 0.04) | |
| Macroalbuminuria (>300) | 260 | 139 | 53.5 | 261 | 117 | 44.8 | 0.0487 | 0.84 | (0.70,<1.00) | 0.71 | (0.50,1.00) | -0.09 | (-0.17, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7862 |
| Low, moderate or high | 1018 | 411 | 40.4 | 1001 | 364 | 36.4 | 0.0640 | 0.90 | (0.81, 1.01) | 0.84 | (0.71,1.01) | -0.04 | (-0.08, 0.00) | |
| Very high | 167 | 92 | 55.1 | 162 | 83 | 51.2 | 0.4835 | 0.93 | (0.76, 1.14) | 0.86 | (0.56,1.32) | -0.04 | (-0.15, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.0604 |
| No | 205 | 87 | 42.4 | 211 | 65 | 30.8 | 0.0138 | 0.73 | (0.56, 0.94) | 0.60 | (0.40,0.90) | -0.12 | (-0.21,-0.02) | |
| Yes | 983 | 417 | 42.4 | 960 | 386 | 40.2 | 0.3220 | 0.95 | (0.85, 1.05) | 0.91 | (0.76,1.09) | -0.02 | (-0.07, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.0412 |
| No | 422 | 189 | 44.8 | 408 | 144 | 35.3 | 0.0053 | 0.79 | (0.67, 0.93) | 0.67 | (0.51,0.89) | -0.09 | (-0.16,-0.03) | |
| Yes | 766 | 315 | 41.1 | 763 | 307 | 40.2 | 0.7241 | 0.98 | (0.87, 1.10) | 0.96 | (0.79,1.18) | -0.01 | (-0.06, 0.04) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8365 |
| No | 629 | 245 | 39.0 | 589 | 205 | 34.8 | 0.1341 | 0.89 | (0.77, 1.04) | 0.84 | (0.66,1.06) | -0.04 | (-0.10, 0.01) | |
| Yes | 559 | 259 | 46.3 | 582 | 246 | 42.3 | 0.1670 | 0.91 | (0.80, 1.04) | 0.85 | (0.67,1.07) | -0.04 | (-0.10, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related events are defined as all events from the SOC `Cardiac Disorders´ and the SOC `Renal and urinary disorders´.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 5 Proportion of patients with severe adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 405 | 34.1 | 1171 | 346 | 29.5 | 0.0179 | 0.87 | (0.77, 0.98) | 0.81 | (0.68,0.96) | -0.05 | (-0.08,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.4683 |
| Male | 864 | 302 | 35.0 | 837 | 247 | 29.5 | 0.0164 | 0.84 | (0.73, 0.97) | 0.78 | (0.64,0.96) | -0.05 | (-0.10,-0.01) | |
| Female | 324 | 103 | 31.8 | 334 | 99 | 29.6 | 0.5501 | 0.93 | (0.74, 1.17) | 0.90 | (0.65,1.26) | -0.02 | (-0.09, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.2352 |
| <65 | 569 | 167 | 29.3 | 547 | 151 | 27.6 | 0.5186 | 0.94 | (0.78, 1.13) | 0.92 | (0.71,1.19) | -0.02 | (-0.07, 0.04) | |
| >=65 | 619 | 238 | 38.4 | 624 | 195 | 31.3 | 0.0077 | 0.81 | (0.70, 0.95) | 0.73 | (0.58,0.92) | -0.07 | (-0.12,-0.02) | |
| Region | | | | | | | | | | | | | | 0.7890 |
| Europe | 468 | 142 | 30.3 | 434 | 122 | 28.1 | 0.4618 | 0.93 | (0.76, 1.14) | 0.90 | (0.67,1.20) | -0.02 | (-0.08, 0.04) | |
| North America | 259 | 108 | 41.7 | 241 | 88 | 36.5 | 0.2354 | 0.88 | (0.70, 1.09) | 0.80 | (0.56,1.15) | -0.05 | (-0.14, 0.03) | |
| Latin America | 177 | 69 | 39.0 | 191 | 59 | 30.9 | 0.1034 | 0.79 | (0.60, 1.05) | 0.70 | (0.45,1.08) | -0.08 | (-0.18, 0.02) | |
| Africa | 50 | 23 | 46.0 | 54 | 17 | 31.5 | 0.1284 | 0.68 | (0.42, 1.12) | 0.54 | (0.24,1.20) | -0.15 | (-0.33, 0.04) | |
| Asia | 234 | 63 | 26.9 | 251 | 60 | 23.9 | 0.4451 | 0.89 | (0.65, 1.21) | 0.85 | (0.57,1.28) | -0.03 | (-0.11, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0821 |
| <30 | 554 | 190 | 34.3 | 566 | 150 | 26.5 | 0.0046 | 0.77 | (0.65, 0.92) | 0.69 | (0.53,0.89) | -0.08 | (-0.13,-0.02) | |
| >=30 | 634 | 215 | 33.9 | 605 | 196 | 32.4 | 0.5713 | 0.96 | (0.82, 1.12) | 0.93 | (0.74,1.18) | -0.02 | (-0.07, 0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2109 |
| <130 | 379 | 132 | 34.8 | 382 | 103 | 27.0 | 0.0189 | 0.77 | (0.62, 0.96) | 0.69 | (0.51,0.94) | -0.08 | (-0.14,-0.01) | |
| >=130 | 809 | 273 | 33.7 | 789 | 243 | 30.8 | 0.2078 | 0.91 | (0.79, 1.05) | 0.87 | (0.71,1.08) | -0.03 | (-0.08, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2209 |
| <75 | 500 | 181 | 36.2 | 500 | 151 | 30.2 | 0.0440 | 0.83 | (0.70,<1.00) | 0.76 | (0.59,0.99) | -0.06 | (-0.12, 0.00) | |
| 75 to <85 | 427 | 135 | 31.6 | 417 | 105 | 25.2 | 0.0382 | 0.80 | (0.64, 0.99) | 0.73 | (0.54,0.98) | -0.06 | (-0.13, 0.00) | |
| >=85 | 261 | 89 | 34.1 | 254 | 90 | 35.4 | 0.7507 | 1.04 | (0.82, 1.32) | 1.06 | (0.74,1.52) | 0.01 | (-0.07, 0.10) | |
| History of heart failure | | | | | | | | | | | | | | 0.4356 |
| No | 1048 | 342 | 32.6 | 1031 | 297 | 28.8 | 0.0587 | 0.88 | (0.78,>1.00) | 0.84 | (0.69,1.01) | -0.04 | (-0.08, 0.00) | |
| Yes | 140 | 63 | 45.0 | 140 | 49 | 35.0 | 0.0877 | 0.78 | (0.58, 1.04) | 0.66 | (0.41,1.06) | -0.10 | (-0.21, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 5 Proportion of patients with severe adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8191 |
| <45 | 179 | 78 | 43.6 | 178 | 69 | 38.8 | 0.3557 | 0.89 | (0.69, 1.14) | 0.82 | (0.54,1.25) | -0.05 | (-0.15, 0.05) | |
| >=45 | 1009 | 327 | 32.4 | 993 | 277 | 27.9 | 0.0278 | 0.86 | (0.75, 0.98) | 0.81 | (0.67,0.98) | -0.05 | (-0.09, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1161 |
| Normal (<30) | 250 | 97 | 38.8 | 257 | 72 | 28.0 | 0.0100 | 0.72 | (0.56, 0.93) | 0.61 | (0.42,0.89) | -0.11 | (-0.19,-0.03) | |
| Microalbuminuria (30 to <=300) | 675 | 211 | 31.3 | 645 | 173 | 26.8 | 0.0760 | 0.86 | (0.72, 1.02) | 0.81 | (0.64,1.02) | -0.04 | (-0.09, 0.00) | |
| Macroalbuminuria (>300) | 260 | 96 | 36.9 | 261 | 99 | 37.9 | 0.8121 | 1.03 | (0.82, 1.28) | 1.04 | (0.73,1.49) | 0.01 | (-0.07, 0.09) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1450 |
| Low, moderate or high | 1018 | 334 | 32.8 | 1001 | 274 | 27.4 | 0.0078 | 0.83 | (0.73, 0.95) | 0.77 | (0.64,0.93) | -0.05 | (-0.09,-0.01) | |
| Very high | 167 | 70 | 41.9 | 162 | 70 | 43.2 | 0.8124 | 1.03 | (0.80, 1.33) | 1.05 | (0.68,1.63) | 0.01 | (-0.09, 0.12) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.8157 |
| No | 205 | 64 | 31.2 | 211 | 59 | 28.0 | 0.4667 | 0.90 | (0.67, 1.21) | 0.86 | (0.56,1.30) | -0.03 | (-0.12, 0.06) | |
| Yes | 983 | 341 | 34.7 | 960 | 287 | 29.9 | 0.0239 | 0.86 | (0.76, 0.98) | 0.80 | (0.66,0.97) | -0.05 | (-0.09,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5604 |
| No | 422 | 137 | 32.5 | 408 | 109 | 26.7 | 0.0698 | 0.82 | (0.67, 1.02) | 0.76 | (0.56,1.02) | -0.06 | (-0.12, 0.00) | |
| Yes | 766 | 268 | 35.0 | 763 | 237 | 31.1 | 0.1027 | 0.89 | (0.77, 1.02) | 0.84 | (0.68,1.04) | -0.04 | (-0.09, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8822 |
| No | 629 | 182 | 28.9 | 589 | 148 | 25.1 | 0.1351 | 0.87 | (0.72, 1.05) | 0.82 | (0.64,1.06) | -0.04 | (-0.09, 0.01) | |
| Yes | 559 | 223 | 39.9 | 582 | 198 | 34.0 | 0.0399 | 0.85 | (0.73, 0.99) | 0.78 | (0.61,0.99) | -0.06 | (-0.11, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 324 | 27.3 | 1171 | 288 | 24.6 | 0.1378 | 0.90 | (0.79,1.03) | 0.87 | (0.72,1.05) | -0.03 | (-0.06, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.6537 |
| Male | 864 | 237 | 27.4 | 837 | 203 | 24.3 | 0.1346 | 0.88 | (0.75,1.04) | 0.85 | (0.68,1.05) | -0.03 | (-0.07, 0.01) | |
| Female | 324 | 87 | 26.9 | 334 | 85 | 25.4 | 0.6822 | 0.95 | (0.73,1.23) | 0.93 | (0.66,1.32) | -0.01 | (-0.08, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.9539 |
| <65 | 569 | 136 | 23.9 | 547 | 117 | 21.4 | 0.3163 | 0.89 | (0.72,1.11) | 0.87 | (0.65,1.15) | -0.03 | (-0.07, 0.02) | |
| >=65 | 619 | 188 | 30.4 | 624 | 171 | 27.4 | 0.2484 | 0.90 | (0.76,1.07) | 0.87 | (0.68,1.11) | -0.03 | (-0.08, 0.02) | |
| Region | | | | | | | | | | | | | | 0.7501 |
| Europe | 468 | 109 | 23.3 | 434 | 99 | 22.8 | 0.8644 | 0.98 | (0.77,1.24) | 0.97 | (0.71,1.33) | 0.00 | (-0.06, 0.05) | |
| North America | 259 | 98 | 37.8 | 241 | 79 | 32.8 | 0.2373 | 0.87 | (0.68,1.10) | 0.80 | (0.55,1.16) | -0.05 | (-0.13, 0.03) | |
| Latin America | 177 | 52 | 29.4 | 191 | 43 | 22.5 | 0.1327 | 0.77 | (0.54,1.09) | 0.70 | (0.44,1.12) | -0.07 | (-0.16, 0.02) | |
| Africa | 50 | 17 | 34.0 | 54 | 15 | 27.8 | 0.4921 | 0.82 | (0.46,1.46) | 0.75 | (0.32,1.72) | -0.06 | (-0.24, 0.12) | |
| Asia | 234 | 48 | 20.5 | 251 | 52 | 20.7 | 0.9557 | 1.01 | (0.71,1.43) | 1.01 | (0.65,1.57) | 0.00 | (-0.07, 0.07) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1347 |
| <30 | 554 | 152 | 27.4 | 566 | 125 | 22.1 | 0.0379 | 0.80 | (0.66,0.99) | 0.75 | (0.57,0.98) | -0.05 | (-0.10, 0.00) | |
| >=30 | 634 | 172 | 27.1 | 605 | 163 | 26.9 | 0.9409 | 0.99 | (0.83,1.19) | 0.99 | (0.77,1.27) | 0.00 | (-0.05, 0.05) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4375 |
| <130 | 379 | 106 | 28.0 | 382 | 89 | 23.3 | 0.1401 | 0.83 | (0.65,1.06) | 0.78 | (0.56,1.08) | -0.05 | (-0.11, 0.02) | |
| >=130 | 809 | 218 | 26.9 | 789 | 199 | 25.2 | 0.4324 | 0.94 | (0.79,1.10) | 0.91 | (0.73,1.14) | -0.02 | (-0.06, 0.03) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3877 |
| <75 | 500 | 149 | 29.8 | 500 | 128 | 25.6 | 0.1378 | 0.86 | (0.70,1.05) | 0.81 | (0.61,1.07) | -0.04 | (-0.10, 0.01) | |
| 75 to <85 | 427 | 106 | 24.8 | 417 | 88 | 21.1 | 0.1989 | 0.85 | (0.66,1.09) | 0.81 | (0.59,1.12) | -0.04 | (-0.09, 0.02) | |
| >=85 | 261 | 69 | 26.4 | 254 | 72 | 28.3 | 0.6270 | 1.07 | (0.81,1.42) | 1.10 | (0.75,1.62) | 0.02 | (-0.06, 0.10) | |
| History of heart failure | | | | | | | | | | | | | | 0.5693 |
| No | 1048 | 273 | 26.0 | 1031 | 246 | 23.9 | 0.2488 | 0.92 | (0.79,1.06) | 0.89 | (0.73,1.09) | -0.02 | (-0.06, 0.02) | |
| Yes | 140 | 51 | 36.4 | 140 | 42 | 30.0 | 0.2535 | 0.82 | (0.59,1.15) | 0.75 | (0.45,1.23) | -0.06 | (-0.17, 0.05) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related events are defined as all events from the SOC `Cardiac Disorders´ and the SOC `Renal and urinary disorders´.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.7690 |
| <45 | 179 | 65 | 36.3 | 178 | 56 | 31.5 | 0.3328 | 0.87 (0.65,1.16) | 0.81 (0.52,1.25) | -0.05 (-0.15, 0.05) | |
| >=45 | 1009 | 259 | 25.7 | 993 | 232 | 23.4 | 0.2306 | 0.91 (0.78,1.06) | 0.88 (0.72,1.08) | -0.02 (-0.06, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.1062 |
| Normal (<30) | 250 | 81 | 32.4 | 257 | 58 | 22.6 | 0.0131 | 0.70 (0.52,0.93) | 0.61 (0.41,0.90) | -0.10 (-0.18,-0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 162 | 24.0 | 645 | 144 | 22.3 | 0.4711 | 0.93 (0.76,1.13) | 0.91 (0.70,1.18) | -0.02 (-0.06, 0.03) | |
| Macroalbuminuria (>300) | 260 | 80 | 30.8 | 261 | 84 | 32.2 | 0.7281 | 1.05 (0.81,1.35) | 1.07 (0.74,1.55) | 0.01 (-0.07, 0.09) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.5490 |
| Low, moderate or high | 1018 | 263 | 25.8 | 1001 | 229 | 22.9 | 0.1217 | 0.89 (0.76,1.03) | 0.85 (0.69,1.04) | -0.03 (-0.07, 0.01) | |
| Very high | 167 | 60 | 35.9 | 162 | 57 | 35.2 | 0.8881 | 0.98 (0.73,1.31) | 0.97 (0.62,1.52) | -0.01 (-0.11, 0.10) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.5696 |
| No | 205 | 52 | 25.4 | 211 | 44 | 20.9 | 0.2748 | 0.82 (0.58,1.17) | 0.78 (0.49,1.22) | -0.05 (-0.13, 0.04) | |
| Yes | 983 | 272 | 27.7 | 960 | 244 | 25.4 | 0.2607 | 0.92 (0.79,1.07) | 0.89 (0.73,1.09) | -0.02 (-0.06, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.2856 |
| No | 422 | 116 | 27.5 | 408 | 91 | 22.3 | 0.0844 | 0.81 (0.64,1.03) | 0.76 (0.55,1.04) | -0.05 (-0.11, 0.01) | |
| Yes | 766 | 208 | 27.2 | 763 | 197 | 25.8 | 0.5542 | 0.95 (0.80,1.12) | 0.93 (0.74,1.17) | -0.01 (-0.06, 0.03) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9280 |
| No | 629 | 149 | 23.7 | 589 | 124 | 21.1 | 0.2703 | 0.89 (0.72,1.10) | 0.86 (0.66,1.13) | -0.03 (-0.07, 0.02) | |
| Yes | 559 | 175 | 31.3 | 582 | 164 | 28.2 | 0.2479 | 0.90 (0.75,1.08) | 0.86 (0.67,1.11) | -0.03 (-0.08, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related events are defined as all events from the SOC `Cardiac Disorders´ and the SOC `Renal and urinary disorders´.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.4.2.2**

R.4.2.2 Adverse events leading to treatment discontinuation

Table R.4.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 273 | 23.0 | 1171 | 244 | 20.8 | 0.2084 | 0.91 | (0.78,1.06) | 0.88 | (0.73,1.07) | -0.02 | (-0.05, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.7123 |
| Male | 864 | 208 | 24.1 | 837 | 180 | 21.5 | 0.2069 | 0.89 | (0.75,1.06) | 0.86 | (0.69,1.08) | -0.03 | (-0.07, 0.01) | |
| Female | 324 | 65 | 20.1 | 334 | 64 | 19.2 | 0.7713 | 0.96 | (0.70,1.30) | 0.94 | (0.64,1.39) | -0.01 | (-0.07, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.6846 |
| <65 | 569 | 113 | 19.9 | 547 | 102 | 18.6 | 0.6077 | 0.94 | (0.74,1.19) | 0.92 | (0.69,1.25) | -0.01 | (-0.06, 0.03) | |
| >=65 | 619 | 160 | 25.8 | 624 | 142 | 22.8 | 0.2038 | 0.88 | (0.72,1.07) | 0.85 | (0.65,1.10) | -0.03 | (-0.08, 0.02) | |
| Region | | | | | | | | | | | | | | 0.5809 |
| Europe | 468 | 97 | 20.7 | 434 | 95 | 21.9 | 0.6699 | 1.06 | (0.82,1.36) | 1.07 | (0.78,1.47) | 0.01 | (-0.04, 0.07) | |
| North America | 259 | 62 | 23.9 | 241 | 52 | 21.6 | 0.5294 | 0.90 | (0.65,1.25) | 0.87 | (0.57,1.33) | -0.02 | (-0.10, 0.05) | |
| Latin America | 177 | 53 | 29.9 | 191 | 48 | 25.1 | 0.3013 | 0.84 | (0.60,1.17) | 0.79 | (0.50,1.24) | -0.05 | (-0.14, 0.04) | |
| Africa | 50 | 11 | 22.0 | 54 | 9 | 16.7 | 0.4905 | 0.76 | (0.34,1.67) | 0.71 | (0.27,1.89) | -0.05 | (-0.21, 0.10) | |
| Asia | 234 | 50 | 21.4 | 251 | 40 | 15.9 | 0.1242 | 0.75 | (0.51,1.09) | 0.70 | (0.44,1.11) | -0.05 | (-0.12, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6237 |
| <30 | 554 | 127 | 22.9 | 566 | 113 | 20.0 | 0.2275 | 0.87 | (0.70,1.09) | 0.84 | (0.63,1.12) | -0.03 | (-0.08, 0.02) | |
| >=30 | 634 | 146 | 23.0 | 605 | 131 | 21.7 | 0.5613 | 0.94 | (0.76,1.16) | 0.92 | (0.71,1.21) | -0.01 | (-0.06, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5950 |
| <130 | 379 | 85 | 22.4 | 382 | 73 | 19.1 | 0.2593 | 0.85 | (0.64,1.13) | 0.82 | (0.58,1.16) | -0.03 | (-0.09, 0.02) | |
| >=130 | 809 | 188 | 23.2 | 789 | 171 | 21.7 | 0.4534 | 0.93 | (0.78,1.12) | 0.91 | (0.72,1.16) | -0.02 | (-0.06, 0.03) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3927 |
| <75 | 500 | 119 | 23.8 | 500 | 110 | 22.0 | 0.4982 | 0.92 | (0.74,1.16) | 0.90 | (0.67,1.21) | -0.02 | (-0.07, 0.03) | |
| 75 to <85 | 427 | 99 | 23.2 | 417 | 77 | 18.5 | 0.0915 | 0.80 | (0.61,1.04) | 0.75 | (0.54,1.05) | -0.05 | (-0.10, 0.01) | |
| >=85 | 261 | 55 | 21.1 | 254 | 57 | 22.4 | 0.7067 | 1.06 | (0.77,1.48) | 1.08 | (0.71,1.65) | 0.01 | (-0.06, 0.08) | |
| History of heart failure | | | | | | | | | | | | | | 0.4762 |
| No | 1048 | 228 | 21.8 | 1031 | 208 | 20.2 | 0.3759 | 0.93 | (0.78,1.10) | 0.91 | (0.74,1.12) | -0.02 | (-0.05, 0.02) | |
| Yes | 140 | 45 | 32.1 | 140 | 36 | 25.7 | 0.2355 | 0.80 | (0.55,1.16) | 0.73 | (0.43,1.23) | -0.06 | (-0.17, 0.04) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3674 |
| <45 | 179 | 59 | 33.0 | 178 | 60 | 33.7 | 0.8810 | 1.02 | (0.76,1.37) | 1.03 | (0.67,1.61) | 0.01 | (-0.09, 0.11) | |
| >=45 | 1009 | 214 | 21.2 | 993 | 184 | 18.5 | 0.1331 | 0.87 | (0.73,1.04) | 0.84 | (0.68,1.05) | -0.03 | (-0.06, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6283 |
| Normal (<30) | 250 | 57 | 22.8 | 257 | 53 | 20.6 | 0.5520 | 0.90 | (0.65,1.26) | 0.88 | (0.58,1.34) | -0.02 | (-0.09, 0.05) | |
| Microalbuminuria (30 to <=300) | 675 | 143 | 21.2 | 645 | 116 | 18.0 | 0.1433 | 0.85 | (0.68,1.06) | 0.82 | (0.62,1.07) | -0.03 | (-0.07, 0.01) | |
| Macroalbuminuria (>300) | 260 | 72 | 27.7 | 261 | 73 | 28.0 | 0.9438 | 1.01 | (0.77,1.33) | 1.01 | (0.69,1.49) | 0.00 | (-0.07, 0.08) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5901 |
| Low, moderate or high | 1018 | 214 | 21.0 | 1001 | 187 | 18.7 | 0.1876 | 0.89 | (0.75,1.06) | 0.86 | (0.69,1.07) | -0.02 | (-0.06, 0.01) | |
| Very high | 167 | 58 | 34.7 | 162 | 55 | 34.0 | 0.8816 | 0.98 | (0.72,1.32) | 0.97 | (0.61,1.52) | -0.01 | (-0.11, 0.09) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.0811 |
| No | 205 | 50 | 24.4 | 211 | 34 | 16.1 | 0.0355 | 0.66 | (0.45,0.98) | 0.60 | (0.37,0.97) | -0.08 | (-0.16,-0.01) | |
| Yes | 983 | 223 | 22.7 | 960 | 210 | 21.9 | 0.6677 | 0.96 | (0.82,1.14) | 0.95 | (0.77,1.18) | -0.01 | (-0.05, 0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1490 |
| No | 422 | 98 | 23.2 | 408 | 73 | 17.9 | 0.0577 | 0.77 | (0.59,1.01) | 0.72 | (0.51,1.01) | -0.05 | (-0.11, 0.00) | |
| Yes | 766 | 175 | 22.8 | 763 | 171 | 22.4 | 0.8391 | 0.98 | (0.81,1.18) | 0.98 | (0.77,1.24) | 0.00 | (-0.05, 0.04) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2423 |
| No | 629 | 128 | 20.3 | 589 | 97 | 16.5 | 0.0811 | 0.81 | (0.64,1.03) | 0.77 | (0.58,1.03) | -0.04 | (-0.08, 0.00) | |
| Yes | 559 | 145 | 25.9 | 582 | 147 | 25.3 | 0.7920 | 0.97 | (0.80,1.19) | 0.96 | (0.74,1.26) | -0.01 | (-0.06, 0.04) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Number of patients | 1188 (100.0) | | | 1171 (100.0) | | |
| Total with adverse events | 273 ( 23.0) | 3028.23 | 9.02 | 244 ( 20.8) | 3034.64 | 8.04 |
| Cardiac disorders | 68 ( 5.7) | 3297.49 | 2.06 | 38 ( 3.2) | 3332.67 | 1.14 |
| Myocardial infarction | 14 ( 1.2) | 3345.02 | 0.42 | 11 ( 0.9) | 3358.54 | 0.33 |
| Acute myocardial infarction | 12 ( 1.0) | 3343.41 | 0.36 | 6 ( 0.5) | 3359.79 | 0.18 |
| Cardiac failure | 10 ( 0.8) | 3342.56 | 0.30 | 8 ( 0.7) | 3363.16 | 0.24 |
| Angina unstable | 2 ( 0.2) | 3350.90 | 0.06 | 6 ( 0.5) | 3358.26 | 0.18 |
| Cardiac arrest | 6 ( 0.5) | 3353.86 | 0.18 | 2 ( 0.2) | 3365.83 | 0.06 |
| Cardio-respiratory arrest | 5 ( 0.4) | 3350.43 | 0.15 | 2 ( 0.2) | 3365.90 | 0.06 |
| Coronary artery disease | 5 ( 0.4) | 3350.90 | 0.15 | 0 | 3366.51 | 0 |
| Cardiac failure congestive | 4 ( 0.3) | 3350.33 | 0.12 | 0 | 3366.51 | 0 |
| Acute coronary syndrome | 3 ( 0.3) | 3352.91 | 0.09 | 0 | 3366.51 | 0 |
| Cardiogenic shock | 1 ( 0.1) | 3353.86 | 0.03 | 2 ( 0.2) | 3366.49 | 0.06 |
| Myocardial ischaemia | 2 ( 0.2) | 3351.68 | 0.06 | 1 ( 0.1) | 3364.47 | 0.03 |
| Ventricular tachycardia | 2 ( 0.2) | 3352.89 | 0.06 | 0 | 3366.51 | 0 |
| Arrhythmia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.51 | 0.03 |
| Atrial fibrillation | 1 ( 0.1) | 3351.36 | 0.03 | 1 ( 0.1) | 3364.09 | 0.03 |
| Cardiac asthma | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.51 | 0.03 |
| Palpitations | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.03 | 0.03 |
| Angina pectoris | 1 ( 0.1) | 3351.29 | 0.03 | 0 | 3366.51 | 0 |
| Arteriosclerosis coronary artery | 1 ( 0.1) | 3350.90 | 0.03 | 0 | 3366.51 | 0 |
| Hypertensive heart disease | 1 ( 0.1) | 3353.72 | 0.03 | 0 | 3366.51 | 0 |
| Nodal arrhythmia | 1 ( 0.1) | 3353.84 | 0.03 | 0 | 3366.51 | 0 |
| Ventricular extrasystoles | 1 ( 0.1) | 3351.49 | 0.03 | 0 | 3366.51 | 0 |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 18.0

Table R.4.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Infections and infestations | 44 ( 3.7) | 3301.41 | 1.33 | 47 ( 4.0) | 3295.54 | 1.43 |
| Urinary tract infection | 6 ( 0.5) | 3344.42 | 0.18 | 11 ( 0.9) | 3350.54 | 0.33 |
| Pneumonia | 11 ( 0.9) | 3346.99 | 0.33 | 8 ( 0.7) | 3354.18 | 0.24 |
| Gastroenteritis | 4 ( 0.3) | 3346.03 | 0.12 | 4 ( 0.3) | 3359.36 | 0.12 |
| Sepsis | 1 ( 0.1) | 3353.78 | 0.03 | 4 ( 0.3) | 3365.43 | 0.12 |
| Infected skin ulcer | 3 ( 0.3) | 3351.02 | 0.09 | 1 ( 0.1) | 3365.70 | 0.03 |
| Diabetic foot infection | 1 ( 0.1) | 3350.75 | 0.03 | 2 ( 0.2) | 3364.85 | 0.06 |
| Erysipelas | 0 | 3353.86 | 0 | 2 ( 0.2) | 3363.97 | 0.06 |
| Wound infection | 0 | 3353.86 | 0 | 2 ( 0.2) | 3363.14 | 0.06 |
| Gangrene | 2 ( 0.2) | 3352.11 | 0.06 | 0 | 3366.51 | 0 |
| Localised infection | 2 ( 0.2) | 3352.83 | 0.06 | 1 ( 0.1) | 3365.23 | 0.03 |
| Nasopharyngitis | 2 ( 0.2) | 3350.72 | 0.06 | 0 | 3366.51 | 0 |
| Respiratory tract infection | 2 ( 0.2) | 3353.46 | 0.06 | 1 ( 0.1) | 3364.33 | 0.03 |
| Abdominal abscess | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.75 | 0.03 |
| Asymptomatic bacteriuria | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.82 | 0.03 |
| Cellulitis | 1 ( 0.1) | 3353.42 | 0.03 | 1 ( 0.1) | 3366.32 | 0.03 |
| Cystitis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.05 | 0.03 |
| Fungal infection | 0 | 3353.86 | 0 | 1 ( 0.1) | 3362.47 | 0.03 |
| Fungal skin infection | 0 | 3353.86 | 0 | 1 ( 0.1) | 3362.47 | 0.03 |
| Genital infection | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.14 | 0.03 |
| Genital infection fungal | 0 | 3353.86 | 0 | 1 ( 0.1) | 3362.70 | 0.03 |
| Influenza | 1 ( 0.1) | 3353.03 | 0.03 | 1 ( 0.1) | 3363.29 | 0.03 |
| Labyrinthitis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.64 | 0.03 |
| Meningitis bacterial | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.88 | 0.03 |
| Myelitis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.33 | 0.03 |
| Osteomyelitis | 1 ( 0.1) | 3351.60 | 0.03 | 1 ( 0.1) | 3365.92 | 0.03 |
| Septic shock | 1 ( 0.1) | 3353.86 | 0.03 | 1 ( 0.1) | 3366.51 | 0.03 |
| Urosepsis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.49 | 0.03 |
| Vulvovaginal candidiasis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.97 | 0.03 |
| Bronchitis | 1 ( 0.1) | 3353.76 | 0.03 | 0 | 3366.51 | 0 |
| Cutaneous larva migrans | 1 ( 0.1) | 3350.53 | 0.03 | 0 | 3366.51 | 0 |
| Gastroenteritis viral | 1 ( 0.1) | 3353.69 | 0.03 | 0 | 3366.51 | 0 |
| Lobar pneumonia | 1 ( 0.1) | 3352.07 | 0.03 | 0 | 3366.51 | 0 |
| Otitis externa | 1 ( 0.1) | 3351.32 | 0.03 | 0 | 3366.51 | 0 |
| Pharyngotonsillitis | 1 ( 0.1) | 3351.12 | 0.03 | 0 | 3366.51 | 0 |
| Pneumonia pneumococcal | 1 ( 0.1) | 3353.84 | 0.03 | 0 | 3366.51 | 0 |
| Pyelonephritis | 1 ( 0.1) | 3353.34 | 0.03 | 0 | 3366.51 | 0 |
| Skin infection | 1 ( 0.1) | 3353.24 | 0.03 | 0 | 3366.51 | 0 |
| Varicella | 1 ( 0.1) | 3352.47 | 0.03 | 0 | 3366.51 | 0 |
| Viral infection | 1 ( 0.1) | 3350.78 | 0.03 | 0 | 3366.51 | 0 |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 18.0

Table R.4.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 16 ( 1.3) | 3335.79 | 0.48 | 32 ( 2.7) | 3333.65 | 0.96 |
| Hepatocellular carcinoma | 1 ( 0.1) | 3353.69 | 0.03 | 3 ( 0.3) | 3363.89 | 0.09 |
| Colon cancer | 1 ( 0.1) | 3353.80 | 0.03 | 2 ( 0.2) | 3366.17 | 0.06 |
| Metastases to bone | 0 | 3353.86 | 0 | 2 ( 0.2) | 3364.18 | 0.06 |
| Pancreatic carcinoma | 0 | 3353.86 | 0 | 2 ( 0.2) | 3365.91 | 0.06 |
| Rectal adenocarcinoma | 0 | 3353.86 | 0 | 2 ( 0.2) | 3363.35 | 0.06 |
| Renal cell carcinoma | 0 | 3353.86 | 0 | 2 ( 0.2) | 3361.61 | 0.06 |
| Squamous cell carcinoma of lung | 1 ( 0.1) | 3352.76 | 0.03 | 2 ( 0.2) | 3366.21 | 0.06 |
| Acute lymphocytic leukaemia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.67 | 0.03 |
| Adenocarcinoma of colon | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.37 | 0.03 |
| Benign pancreatic neoplasm | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.83 | 0.03 |
| Benign uterine neoplasm | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.44 | 0.03 |
| Brain neoplasm | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.42 | 0.03 |
| Clear cell renal cell carcinoma | 1 ( 0.1) | 3353.68 | 0.03 | 1 ( 0.1) | 3366.00 | 0.03 |
| Fibrous histiocytoma | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.33 | 0.03 |
| Genital neoplasm malignant female | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.54 | 0.03 |
| Hepatic neoplasm | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.42 | 0.03 |
| Lung adenocarcinoma | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.32 | 0.03 |
| Lung cancer metastatic | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.48 | 0.03 |
| Lymphoma | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.40 | 0.03 |
| Meningioma | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.81 | 0.03 |
| Metastases to liver | 1 ( 0.1) | 3353.35 | 0.03 | 1 ( 0.1) | 3366.43 | 0.03 |
| Metastases to lung | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.26 | 0.03 |
| Prostate cancer | 1 ( 0.1) | 3352.28 | 0.03 | 1 ( 0.1) | 3365.13 | 0.03 |
| Rectal cancer | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.00 | 0.03 |
| Renal cancer metastatic | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.26 | 0.03 |
| Small cell lung cancer | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.43 | 0.03 |
| Splenic marginal zone lymphoma | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.84 | 0.03 |
| Squamous cell carcinoma of the oral cavity | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.17 | 0.03 |
| Adenocarcinoma gastric | 1 ( 0.1) | 3353.65 | 0.03 | 0 | 3366.51 | 0 |
| Adenocarcinoma pancreas | 1 ( 0.1) | 3353.74 | 0.03 | 0 | 3366.51 | 0 |
| B-cell lymphoma | 1 ( 0.1) | 3352.16 | 0.03 | 0 | 3366.51 | 0 |
| Bone cancer | 1 ( 0.1) | 3352.36 | 0.03 | 0 | 3366.51 | 0 |
| Colon neoplasm | 1 ( 0.1) | 3350.71 | 0.03 | 0 | 3366.51 | 0 |
| Lung neoplasm malignant | 1 ( 0.1) | 3353.31 | 0.03 | 0 | 3366.51 | 0 |
| Myelodysplastic syndrome | 1 ( 0.1) | 3353.20 | 0.03 | 0 | 3366.51 | 0 |
| Oesophageal adenocarcinoma | 1 ( 0.1) | 3353.35 | 0.03 | 0 | 3366.51 | 0 |

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Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 18.0

Table R.4.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (cont.) | | | | | | |
| Plasma cell myeloma | 1 ( 0.1) | 3353.40 | 0.03 | 0 | 3366.51 | 0 |
| Renal cell carcinoma stage II | 1 ( 0.1) | 3350.90 | 0.03 | 0 | 3366.51 | 0 |
| Small cell carcinoma | 1 ( 0.1) | 3350.66 | 0.03 | 0 | 3366.51 | 0 |
| Renal and urinary disorders | 32 ( 2.7) | 3310.81 | 0.97 | 29 ( 2.5) | 3315.83 | 0.87 |
| Renal impairment | 9 ( 0.8) | 3342.41 | 0.27 | 9 ( 0.8) | 3348.76 | 0.27 |
| Renal failure | 7 ( 0.6) | 3343.81 | 0.21 | 3 ( 0.3) | 3363.98 | 0.09 |
| Acute kidney injury | 5 ( 0.4) | 3346.77 | 0.15 | 4 ( 0.3) | 3358.99 | 0.12 |
| Chronic kidney disease | 4 ( 0.3) | 3351.33 | 0.12 | 4 ( 0.3) | 3361.80 | 0.12 |
| Diabetic nephropathy | 4 ( 0.3) | 3348.96 | 0.12 | 2 ( 0.2) | 3361.79 | 0.06 |
| Dysuria | 0 | 3353.86 | 0 | 2 ( 0.2) | 3362.21 | 0.06 |
| Pollakiuria | 1 ( 0.1) | 3350.48 | 0.03 | 2 ( 0.2) | 3362.03 | 0.06 |
| Haematuria | 1 ( 0.1) | 3353.76 | 0.03 | 1 ( 0.1) | 3365.54 | 0.03 |
| Hydronephrosis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.93 | 0.03 |
| Nocturia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.80 | 0.03 |
| Proteinuria | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.56 | 0.03 |
| Albuminuria | 1 ( 0.1) | 3352.18 | 0.03 | 0 | 3366.51 | 0 |
| Calculus ureteric | 1 ( 0.1) | 3352.15 | 0.03 | 0 | 3366.51 | 0 |
| Calculus urinary | 1 ( 0.1) | 3351.32 | 0.03 | 0 | 3366.51 | 0 |
| Nephropathy | 1 ( 0.1) | 3352.68 | 0.03 | 0 | 3366.51 | 0 |
| Renal cyst | 1 ( 0.1) | 3351.32 | 0.03 | 0 | 3366.51 | 0 |
| Urinary retention | 1 ( 0.1) | 3352.94 | 0.03 | 0 | 3366.51 | 0 |

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MedDRA version: 18.0

Table R.4.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Nervous system disorders | 23 ( 1.9) | 3327.51 | 0.69 | 31 ( 2.6) | 3327.57 | 0.93 |
| Cerebrovascular accident | 2 ( 0.2) | 3352.76 | 0.06 | 8 ( 0.7) | 3359.13 | 0.24 |
| Ischaemic stroke | 2 ( 0.2) | 3350.60 | 0.06 | 7 ( 0.6) | 3359.24 | 0.21 |
| Haemorrhagic stroke | 4 ( 0.3) | 3352.95 | 0.12 | 0 | 3366.51 | 0 |
| Dizziness | 2 ( 0.2) | 3350.08 | 0.06 | 3 ( 0.3) | 3358.43 | 0.09 |
| Carotid artery stenosis | 2 ( 0.2) | 3353.15 | 0.06 | 0 | 3366.51 | 0 |
| Subarachnoid haemorrhage | 2 ( 0.2) | 3351.70 | 0.06 | 0 | 3366.51 | 0 |
| Syncope | 2 ( 0.2) | 3349.47 | 0.06 | 0 | 3366.51 | 0 |
| Brain stem haemorrhage | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.51 | 0.03 |
| Brain stem infarction | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.17 | 0.03 |
| Carotid arteriosclerosis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.42 | 0.03 |
| Cerebral infarction | 1 ( 0.1) | 3352.80 | 0.03 | 1 ( 0.1) | 3364.28 | 0.03 |
| Cerebral ischaemia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.29 | 0.03 |
| Cerebrovascular disorder | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.51 | 0.03 |
| Dementia Alzheimer's type | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.63 | 0.03 |
| Headache | 1 ( 0.1) | 3350.20 | 0.03 | 1 ( 0.1) | 3366.25 | 0.03 |
| Lacunar infarction | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.70 | 0.03 |
| Paraplegia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.16 | 0.03 |
| Prosopagnosia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.25 | 0.03 |
| Seizure | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.00 | 0.03 |
| Thalamic infarction | 1 ( 0.1) | 3352.63 | 0.03 | 1 ( 0.1) | 3364.41 | 0.03 |
| Tremor | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.15 | 0.03 |
| Amnesia | 1 ( 0.1) | 3352.88 | 0.03 | 0 | 3366.51 | 0 |
| Cerebrovascular insufficiency | 1 ( 0.1) | 3351.80 | 0.03 | 0 | 3366.51 | 0 |
| Dementia | 1 ( 0.1) | 3353.01 | 0.03 | 0 | 3366.51 | 0 |
| Intercostal neuralgia | 1 ( 0.1) | 3353.63 | 0.03 | 0 | 3366.51 | 0 |

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MedDRA version: 18.0

Table R.4.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Gastrointestinal disorders | 25 ( 2.1) | 3318.54 | 0.75 | 16 ( 1.4) | 3334.66 | 0.48 |
| Diarrhoea | 7 ( 0.6) | 3345.73 | 0.21 | 2 ( 0.2) | 3361.10 | 0.06 |
| Vomiting | 5 ( 0.4) | 3351.18 | 0.15 | 0 | 3366.51 | 0 |
| Abdominal pain | 1 ( 0.1) | 3353.86 | 0.03 | 2 ( 0.2) | 3361.56 | 0.06 |
| Constipation | 2 ( 0.2) | 3350.56 | 0.06 | 1 ( 0.1) | 3364.12 | 0.03 |
| Gastric ulcer | 2 ( 0.2) | 3346.19 | 0.06 | 0 | 3366.51 | 0 |
| Gastritis | 2 ( 0.2) | 3351.44 | 0.06 | 0 | 3366.51 | 0 |
| Abdominal discomfort | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.57 | 0.03 |
| Ascites | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.44 | 0.03 |
| Diverticulum intestinal | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.81 | 0.03 |
| Gastritis erosive | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.81 | 0.03 |
| Gastrointestinal angiodysplasia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.09 | 0.03 |
| Gastrointestinal haemorrhage | 1 ( 0.1) | 3353.85 | 0.03 | 1 ( 0.1) | 3363.81 | 0.03 |
| Hiatus hernia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.81 | 0.03 |
| Ileus | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.64 | 0.03 |
| Intestinal ischaemia | 1 ( 0.1) | 3352.11 | 0.03 | 1 ( 0.1) | 3366.51 | 0.03 |
| Oesophagitis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.81 | 0.03 |
| Pancreatitis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.17 | 0.03 |
| Pancreatitis acute | 0 | 3353.86 | 0 | 1 ( 0.1) | 3362.95 | 0.03 |
| Thrombosis mesenteric vessel | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.51 | 0.03 |
| Tongue dry | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.47 | 0.03 |
| Varices oesophageal | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.40 | 0.03 |
| Colon dysplasia | 1 ( 0.1) | 3350.71 | 0.03 | 0 | 3366.51 | 0 |
| Dry mouth | 1 ( 0.1) | 3351.96 | 0.03 | 0 | 3366.51 | 0 |
| Duodenal ulcer | 1 ( 0.1) | 3350.14 | 0.03 | 0 | 3366.51 | 0 |
| Dyspepsia | 1 ( 0.1) | 3351.52 | 0.03 | 0 | 3366.51 | 0 |
| Dysphagia | 1 ( 0.1) | 3351.40 | 0.03 | 0 | 3366.51 | 0 |
| Epigastric discomfort | 1 ( 0.1) | 3352.41 | 0.03 | 0 | 3366.51 | 0 |
| Erosive duodenitis | 1 ( 0.1) | 3351.73 | 0.03 | 0 | 3366.51 | 0 |
| Gastritis haemorrhagic | 1 ( 0.1) | 3353.85 | 0.03 | 0 | 3366.51 | 0 |
| Gastrooesophageal reflux disease | 1 ( 0.1) | 3350.14 | 0.03 | 0 | 3366.51 | 0 |
| Intestinal obstruction | 1 ( 0.1) | 3352.90 | 0.03 | 0 | 3366.51 | 0 |
| Small intestinal obstruction | 1 ( 0.1) | 3352.64 | 0.03 | 0 | 3366.51 | 0 |
| Upper gastrointestinal haemorrhage | 1 ( 0.1) | 3353.85 | 0.03 | 0 | 3366.51 | 0 |

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MedDRA version: 18.0

Table R.4.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| General disorders and administration site conditions | 19 ( 1.6) | 3336.79 | 0.57 | 19 ( 1.6) | 3355.61 | 0.57 |
| Sudden death | 2 ( 0.2) | 3353.86 | 0.06 | 6 ( 0.5) | 3366.51 | 0.18 |
| Death | 6 ( 0.5) | 3353.86 | 0.18 | 5 ( 0.4) | 3366.51 | 0.15 |
| Cardiac death | 2 ( 0.2) | 3353.86 | 0.06 | 2 ( 0.2) | 3366.51 | 0.06 |
| Oedema peripheral | 2 ( 0.2) | 3350.08 | 0.06 | 1 ( 0.1) | 3364.79 | 0.03 |
| Sudden cardiac death | 2 ( 0.2) | 3353.86 | 0.06 | 1 ( 0.1) | 3366.51 | 0.03 |
| Asthenia | 1 ( 0.1) | 3352.72 | 0.03 | 1 ( 0.1) | 3364.77 | 0.03 |
| Chest pain | 1 ( 0.1) | 3351.32 | 0.03 | 1 ( 0.1) | 3364.40 | 0.03 |
| Dysplasia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.41 | 0.03 |
| Fatigue | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.29 | 0.03 |
| Chest discomfort | 1 ( 0.1) | 3352.72 | 0.03 | 0 | 3366.51 | 0 |
| Discomfort | 1 ( 0.1) | 3351.05 | 0.03 | 0 | 3366.51 | 0 |
| Extravasation | 1 ( 0.1) | 3352.72 | 0.03 | 0 | 3366.51 | 0 |
| Oedema | 1 ( 0.1) | 3350.25 | 0.03 | 0 | 3366.51 | 0 |
| Peripheral swelling | 1 ( 0.1) | 3351.79 | 0.03 | 0 | 3366.51 | 0 |
| Vascular disorders | 17 ( 1.4) | 3332.83 | 0.51 | 7 ( 0.6) | 3351.15 | 0.21 |
| Peripheral ischaemia | 4 ( 0.3) | 3349.12 | 0.12 | 0 | 3366.51 | 0 |
| Peripheral arterial occlusive disease | 2 ( 0.2) | 3350.97 | 0.06 | 2 ( 0.2) | 3361.99 | 0.06 |
| Hypotension | 2 ( 0.2) | 3349.66 | 0.06 | 1 ( 0.1) | 3364.40 | 0.03 |
| Aortic stenosis | 1 ( 0.1) | 3353.61 | 0.03 | 1 ( 0.1) | 3364.38 | 0.03 |
| Extremity necrosis | 1 ( 0.1) | 3353.82 | 0.03 | 1 ( 0.1) | 3363.93 | 0.03 |
| Femoral artery occlusion | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.10 | 0.03 |
| Thrombosis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.91 | 0.03 |
| Embolism | 1 ( 0.1) | 3353.86 | 0.03 | 0 | 3366.51 | 0 |
| Hypertension | 1 ( 0.1) | 3350.76 | 0.03 | 0 | 3366.51 | 0 |
| Hypertensive crisis | 1 ( 0.1) | 3352.33 | 0.03 | 0 | 3366.51 | 0 |
| Hypovolaemic shock | 1 ( 0.1) | 3353.85 | 0.03 | 0 | 3366.51 | 0 |
| Peripheral vascular disorder | 1 ( 0.1) | 3353.65 | 0.03 | 0 | 3366.51 | 0 |
| Varicose ulceration | 1 ( 0.1) | 3352.54 | 0.03 | 0 | 3366.51 | 0 |
| Venous occlusion | 1 ( 0.1) | 3351.07 | 0.03 | 0 | 3366.51 | 0 |

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Table R.4.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Injury, poisoning and procedural complications | 16 ( 1.3) | 3335.76 | 0.48 | 7 ( 0.6) | 3358.99 | 0.21 |
| Fall | 2 ( 0.2) | 3350.98 | 0.06 | 0 | 3366.51 | 0 |
| Chemical poisoning | 1 ( 0.1) | 3353.85 | 0.03 | 1 ( 0.1) | 3366.51 | 0.03 |
| Gun shot wound | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.90 | 0.03 |
| Lower limb fracture | 1 ( 0.1) | 3353.46 | 0.03 | 1 ( 0.1) | 3365.97 | 0.03 |
| Peripheral artery restenosis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.58 | 0.03 |
| Road traffic accident | 1 ( 0.1) | 3352.39 | 0.03 | 1 ( 0.1) | 3365.97 | 0.03 |
| Spinal column injury | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.16 | 0.03 |
| Subdural haematoma | 1 ( 0.1) | 3351.70 | 0.03 | 1 ( 0.1) | 3366.00 | 0.03 |
| Vascular graft occlusion | 1 ( 0.1) | 3352.25 | 0.03 | 1 ( 0.1) | 3365.95 | 0.03 |
| Ankle fracture | 1 ( 0.1) | 3353.03 | 0.03 | 0 | 3366.51 | 0 |
| Contusion | 1 ( 0.1) | 3351.70 | 0.03 | 0 | 3366.51 | 0 |
| Facial bones fracture | 1 ( 0.1) | 3351.88 | 0.03 | 0 | 3366.51 | 0 |
| Femur fracture | 1 ( 0.1) | 3353.60 | 0.03 | 0 | 3366.51 | 0 |
| Fibula fracture | 1 ( 0.1) | 3351.44 | 0.03 | 0 | 3366.51 | 0 |
| Foot fracture | 1 ( 0.1) | 3350.98 | 0.03 | 0 | 3366.51 | 0 |
| Gastrointestinal anastomotic complication | 1 ( 0.1) | 3353.86 | 0.03 | 0 | 3366.51 | 0 |
| Head injury | 1 ( 0.1) | 3352.73 | 0.03 | 0 | 3366.51 | 0 |
| Hip fracture | 1 ( 0.1) | 3352.39 | 0.03 | 0 | 3366.51 | 0 |
| Meniscus injury | 1 ( 0.1) | 3353.36 | 0.03 | 0 | 3366.51 | 0 |
| Radius fracture | 1 ( 0.1) | 3350.98 | 0.03 | 0 | 3366.51 | 0 |
| Tibia fracture | 1 ( 0.1) | 3351.44 | 0.03 | 0 | 3366.51 | 0 |
| Traumatic intracranial haemorrhage | 1 ( 0.1) | 3353.62 | 0.03 | 0 | 3366.51 | 0 |
| Wound | 1 ( 0.1) | 3351.60 | 0.03 | 0 | 3366.51 | 0 |
| Skin and subcutaneous tissue disorders | 11 ( 0.9) | 3336.92 | 0.33 | 13 ( 1.1) | 3347.15 | 0.39 |
| Diabetic foot | 4 ( 0.3) | 3347.38 | 0.12 | 5 ( 0.4) | 3357.54 | 0.15 |
| Rash | 0 | 3353.86 | 0 | 2 ( 0.2) | 3361.30 | 0.06 |
| Skin ulcer | 2 ( 0.2) | 3352.70 | 0.06 | 2 ( 0.2) | 3365.64 | 0.06 |
| Dermatitis | 2 ( 0.2) | 3348.93 | 0.06 | 0 | 3366.51 | 0 |
| Dermatitis allergic | 1 ( 0.1) | 3352.60 | 0.03 | 1 ( 0.1) | 3364.55 | 0.03 |
| Eczema | 1 ( 0.1) | 3351.48 | 0.03 | 1 ( 0.1) | 3364.96 | 0.03 |
| Erythrodermic psoriasis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.32 | 0.03 |
| Palmar-plantar erythrodysaesthesia syndrome | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.80 | 0.03 |
| Pruritus | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.44 | 0.03 |
| Skin necrosis | 1 ( 0.1) | 3353.11 | 0.03 | 0 | 3366.51 | 0 |

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| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Investigations | 12 ( 1.0) | 3336.73 | 0.36 | 8 ( 0.7) | 3352.25 | 0.24 |
| Blood creatinine increased | 6 ( 0.5) | 3346.10 | 0.18 | 4 ( 0.3) | 3362.78 | 0.12 |
| Lipase increased | 3 ( 0.3) | 3346.32 | 0.09 | 0 | 3366.51 | 0 |
| Blood alkaline phosphatase increased | 1 ( 0.1) | 3353.78 | 0.03 | 1 ( 0.1) | 3365.73 | 0.03 |
| Blood creatine phosphokinase increased | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.47 | 0.03 |
| Eosinophil count increased | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.82 | 0.03 |
| Gamma-glutamyltransferase increased | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.73 | 0.03 |
| Glomerular filtration rate decreased | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.48 | 0.03 |
| Weight decreased | 0 | 3353.86 | 0 | 1 ( 0.1) | 3362.51 | 0.03 |
| Alanine aminotransferase increased | 1 ( 0.1) | 3353.78 | 0.03 | 0 | 3366.51 | 0 |
| Aspartate aminotransferase increased | 1 ( 0.1) | 3353.78 | 0.03 | 0 | 3366.51 | 0 |
| Blood potassium increased | 1 ( 0.1) | 3352.10 | 0.03 | 0 | 3366.51 | 0 |
| Troponin increased | 1 ( 0.1) | 3353.85 | 0.03 | 0 | 3366.51 | 0 |
| Respiratory, thoracic and mediastinal disorders | 12 ( 1.0) | 3340.42 | 0.36 | 7 ( 0.6) | 3359.00 | 0.21 |
| Acute pulmonary oedema | 1 ( 0.1) | 3353.86 | 0.03 | 3 ( 0.3) | 3363.53 | 0.09 |
| Dyspnoea | 3 ( 0.3) | 3346.26 | 0.09 | 1 ( 0.1) | 3364.31 | 0.03 |
| Respiratory failure | 3 ( 0.3) | 3353.01 | 0.09 | 0 | 3366.51 | 0 |
| Acute respiratory failure | 0 | 3353.86 | 0 | 2 ( 0.2) | 3365.49 | 0.06 |
| Acute respiratory distress syndrome | 2 ( 0.2) | 3353.80 | 0.06 | 0 | 3366.51 | 0 |
| Chronic obstructive pulmonary disease | 1 ( 0.1) | 3351.20 | 0.03 | 1 ( 0.1) | 3365.21 | 0.03 |
| Pulmonary embolism | 1 ( 0.1) | 3351.89 | 0.03 | 0 | 3366.51 | 0 |
| Upper respiratory tract congestion | 1 ( 0.1) | 3353.54 | 0.03 | 0 | 3366.51 | 0 |
| Metabolism and nutrition disorders | 7 ( 0.6) | 3340.87 | 0.21 | 11 ( 0.9) | 3353.57 | 0.33 |
| Hyperkalaemia | 1 ( 0.1) | 3352.20 | 0.03 | 3 ( 0.3) | 3361.95 | 0.09 |
| Obesity | 3 ( 0.3) | 3348.57 | 0.09 | 1 ( 0.1) | 3365.71 | 0.03 |
| Diabetes mellitus inadequate control | 0 | 3353.86 | 0 | 2 ( 0.2) | 3363.54 | 0.06 |
| Diabetic ketoacidosis | 0 | 3353.86 | 0 | 2 ( 0.2) | 3366.00 | 0.06 |
| Decreased appetite | 2 ( 0.2) | 3351.01 | 0.06 | 0 | 3366.51 | 0 |
| Diabetic complication | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.69 | 0.03 |
| Hypervolaemia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.36 | 0.03 |
| Hypoglycaemia | 1 ( 0.1) | 3350.65 | 0.03 | 1 ( 0.1) | 3364.40 | 0.03 |
| Dehydration | 1 ( 0.1) | 3353.74 | 0.03 | 0 | 3366.51 | 0 |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 18.0

Table R.4.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Musculoskeletal and connective tissue disorders | 9 ( 0.8) | 3339.38 | 0.27 | 4 ( 0.3) | 3358.81 | 0.12 |
| Musculoskeletal pain | 2 ( 0.2) | 3352.36 | 0.06 | 0 | 3366.51 | 0 |
| Osteoarthritis | 2 ( 0.2) | 3349.64 | 0.06 | 1 ( 0.1) | 3364.13 | 0.03 |
| Costochondritis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.53 | 0.03 |
| Muscular weakness | 1 ( 0.1) | 3350.27 | 0.03 | 1 ( 0.1) | 3365.82 | 0.03 |
| Spinal column stenosis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.87 | 0.03 |
| Arthralgia | 1 ( 0.1) | 3350.80 | 0.03 | 0 | 3366.51 | 0 |
| Back pain | 1 ( 0.1) | 3353.77 | 0.03 | 0 | 3366.51 | 0 |
| Osteoporotic fracture | 1 ( 0.1) | 3353.62 | 0.03 | 0 | 3366.51 | 0 |
| Rhabdomyolysis | 1 ( 0.1) | 3352.07 | 0.03 | 0 | 3366.51 | 0 |
| Reproductive system and breast disorders | 2 ( 0.2) | 3351.63 | 0.06 | 8 ( 0.7) | 3351.99 | 0.24 |
| Balanoposthitis | 0 | 3353.86 | 0 | 2 ( 0.2) | 3363.03 | 0.06 |
| Genital tract inflammation | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.89 | 0.03 |
| Penile swelling | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.00 | 0.03 |
| Prostatitis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.00 | 0.03 |
| Pruritus genital | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.30 | 0.03 |
| Vulvovaginal burning sensation | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.02 | 0.03 |
| Vulvovaginal pruritus | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.84 | 0.03 |
| Atrophic vulvovaginitis | 1 ( 0.1) | 3351.74 | 0.03 | 0 | 3366.51 | 0 |
| Genital discomfort | 1 ( 0.1) | 3353.75 | 0.03 | 0 | 3366.51 | 0 |
| Hepatobiliary disorders | 6 ( 0.5) | 3343.49 | 0.18 | 6 ( 0.5) | 3358.50 | 0.18 |
| Cholecystitis acute | 1 ( 0.1) | 3353.75 | 0.03 | 2 ( 0.2) | 3364.76 | 0.06 |
| Hypertransaminasaemia | 2 ( 0.2) | 3346.86 | 0.06 | 0 | 3366.51 | 0 |
| Bile duct stone | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.78 | 0.03 |
| Cholecystitis | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.15 | 0.03 |
| Cholelithiasis | 1 ( 0.1) | 3353.11 | 0.03 | 1 ( 0.1) | 3364.46 | 0.03 |
| Liver injury | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.41 | 0.03 |
| Cholangitis | 1 ( 0.1) | 3352.44 | 0.03 | 0 | 3366.51 | 0 |
| Hepatic failure | 1 ( 0.1) | 3353.66 | 0.03 | 0 | 3366.51 | 0 |
| Hepatic function abnormal | 1 ( 0.1) | 3352.20 | 0.03 | 0 | 3366.51 | 0 |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 18.0

Table R.4.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Psychiatric disorders | 6 ( 0.5) | 3345.02 | 0.18 | 1 ( 0.1) | 3366.51 | 0.03 |
| Depression | 2 ( 0.2) | 3351.13 | 0.06 | 0 | 3366.51 | 0 |
| Suicide attempt | 1 ( 0.1) | 3352.94 | 0.03 | 1 ( 0.1) | 3366.51 | 0.03 |
| Confusional state | 1 ( 0.1) | 3353.31 | 0.03 | 0 | 3366.51 | 0 |
| Insomnia | 1 ( 0.1) | 3352.99 | 0.03 | 0 | 3366.51 | 0 |
| Mood swings | 1 ( 0.1) | 3350.07 | 0.03 | 0 | 3366.51 | 0 |
| Blood and lymphatic system disorders | 1 ( 0.1) | 3351.73 | 0.03 | 3 ( 0.3) | 3359.69 | 0.09 |
| Anaemia | 1 ( 0.1) | 3351.73 | 0.03 | 2 ( 0.2) | 3361.70 | 0.06 |
| Thrombocytopenia | 0 | 3353.86 | 0 | 1 ( 0.1) | 3364.50 | 0.03 |
| Ear and labyrinth disorders | 3 ( 0.3) | 3347.81 | 0.09 | 1 ( 0.1) | 3364.92 | 0.03 |
| Vertigo | 2 ( 0.2) | 3350.90 | 0.06 | 1 ( 0.1) | 3364.92 | 0.03 |
| Tinnitus | 1 ( 0.1) | 3350.76 | 0.03 | 0 | 3366.51 | 0 |
| Eye disorders | 2 ( 0.2) | 3350.06 | 0.06 | 2 ( 0.2) | 3363.36 | 0.06 |
| Retinal artery occlusion | 0 | 3353.86 | 0 | 1 ( 0.1) | 3363.63 | 0.03 |
| Vision blurred | 0 | 3353.86 | 0 | 1 ( 0.1) | 3366.25 | 0.03 |
| Blindness | 1 ( 0.1) | 3351.57 | 0.03 | 0 | 3366.51 | 0 |
| Cataract | 1 ( 0.1) | 3352.34 | 0.03 | 0 | 3366.51 | 0 |
| Papilloedema | 1 ( 0.1) | 3351.57 | 0.03 | 0 | 3366.51 | 0 |
| Immune system disorders | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.91 | 0.03 |
| Drug hypersensitivity | 0 | 3353.86 | 0 | 1 ( 0.1) | 3365.91 | 0.03 |
| Surgical and medical procedures | 1 ( 0.1) | 3352.74 | 0.03 | 1 ( 0.1) | 3362.83 | 0.03 |
| Coronary artery bypass | 1 ( 0.1) | 3352.74 | 0.03 | 1 ( 0.1) | 3362.83 | 0.03 |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 18.0

**R.4.2.3**

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Lower Limb Amputations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 32 | 2.7 | 1171 | 32 | 2.7 | 0.9534 | 1.01 | ( 0.63, 1.64) | 1.01 | ( 0.62, 1.67) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0921 |
| Male | 864 | 28 | 3.2 | 837 | 22 | 2.6 | 0.4548 | 0.81 | ( 0.47, 1.41) | 0.81 | ( 0.46, 1.42) | -0.01 | (-0.02, 0.01) | |
| Female | 324 | 4 | 1.2 | 334 | 10 | 3.0 | 0.1179 | 2.43 | ( 0.77, 7.65) | 2.47 | ( 0.77, 7.95) | 0.02 | ( 0.00, 0.04) | |
| Age [years] | | | | | | | | | | | | | | 0.3882 |
| <65 | 569 | 17 | 3.0 | 547 | 20 | 3.7 | 0.5329 | 1.22 | ( 0.65, 2.31) | 1.23 | ( 0.64, 2.38) | 0.01 | (-0.01, 0.03) | |
| >=65 | 619 | 15 | 2.4 | 624 | 12 | 1.9 | 0.5453 | 0.79 | ( 0.37, 1.68) | 0.79 | ( 0.37, 1.70) | -0.01 | (-0.02, 0.01) | |
| Region | | | | | | | | | | | | | | 0.5205 |
| Europe | 468 | 15 | 3.2 | 434 | 8 | 1.8 | 0.1948 | 0.58 | ( 0.25, 1.34) | 0.57 | ( 0.24, 1.35) | -0.01 | (-0.03, 0.01) | |
| North America | 259 | 3 | 1.2 | 241 | 4 | 1.7 | 0.6335 | 1.43 | ( 0.32, 6.34) | 1.44 | ( 0.32, 6.50) | 0.01 | (-0.02, 0.03) | |
| Latin America | 177 | 8 | 4.5 | 191 | 12 | 6.3 | 0.4561 | 1.39 | ( 0.58, 3.32) | 1.42 | ( 0.56, 3.55) | 0.02 | (-0.03, 0.06) | |
| Africa | 50 | 1 | 2.0 | 54 | 3 | 5.6 | 0.3462 | 2.78 | ( 0.30,25.84) | 2.88 | ( 0.29,28.66) | 0.04 | (-0.04, 0.11) | |
| Asia | 234 | 5 | 2.1 | 251 | 5 | 2.0 | 0.9108 | 0.93 | ( 0.27, 3.18) | 0.93 | ( 0.27, 3.26) | 0.00 | (-0.03, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7116 |
| <30 | 554 | 16 | 2.9 | 566 | 18 | 3.2 | 0.7757 | 1.10 | ( 0.57, 2.14) | 1.10 | ( 0.56, 2.19) | 0.00 | (-0.02, 0.02) | |
| >=30 | 634 | 16 | 2.5 | 605 | 14 | 2.3 | 0.8104 | 0.92 | ( 0.45, 1.86) | 0.91 | ( 0.44, 1.89) | 0.00 | (-0.02, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1576 |
| <130 | 379 | 5 | 1.3 | 382 | 10 | 2.6 | 0.1976 | 1.98 | ( 0.68, 5.75) | 2.01 | ( 0.68, 5.94) | 0.01 | (-0.01, 0.03) | |
| >=130 | 809 | 27 | 3.3 | 789 | 22 | 2.8 | 0.5244 | 0.84 | ( 0.48, 1.45) | 0.83 | ( 0.47, 1.47) | -0.01 | (-0.02, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0905 |
| <75 | 500 | 10 | 2.0 | 500 | 12 | 2.4 | 0.6663 | 1.20 | ( 0.52, 2.75) | 1.20 | ( 0.52, 2.81) | 0.00 | (-0.01, 0.02) | |
| 75 to <85 | 427 | 15 | 3.5 | 417 | 7 | 1.7 | 0.0945 | 0.48 | ( 0.20, 1.16) | 0.47 | ( 0.19, 1.16) | -0.02 | (-0.04, 0.00) | |
| >=85 | 261 | 7 | 2.7 | 254 | 13 | 5.1 | 0.1525 | 1.91 | ( 0.77, 4.71) | 1.96 | ( 0.77, 4.99) | 0.02 | (-0.01, 0.06) | |
| History of heart failure | | | | | | | | | | | | | | 0.7172 |
| No | 1048 | 26 | 2.5 | 1031 | 27 | 2.6 | 0.8419 | 1.06 | ( 0.62, 1.80) | 1.06 | ( 0.61, 1.82) | 0.00 | (-0.01, 0.01) | |
| Yes | 140 | 6 | 4.3 | 140 | 5 | 3.6 | 0.7584 | 0.83 | ( 0.26, 2.67) | 0.83 | ( 0.25, 2.78) | -0.01 | (-0.05, 0.04) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Lower Limb Amputations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5063 |
| <45 | 179 | 7 | 3.9 | 178 | 5 | 2.8 | 0.5636 | 0.72 | ( 0.23, 2.22) | 0.71 | ( 0.22, 2.28) | -0.01 | (-0.05, 0.03) | |
| >=45 | 1009 | 25 | 2.5 | 993 | 27 | 2.7 | 0.7343 | 1.10 | ( 0.64, 1.88) | 1.10 | ( 0.63, 1.91) | 0.00 | (-0.01, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1390 |
| Normal (<30) | 250 | 6 | 2.4 | 257 | 2 | 0.8 | 0.1429 | 0.32 | ( 0.07, 1.59) | 0.32 | ( 0.06, 1.60) | -0.02 | (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 8 | 1.2 | 645 | 14 | 2.2 | 0.1622 | 1.83 | ( 0.77, 4.34) | 1.85 | ( 0.77, 4.44) | 0.01 | ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 260 | 18 | 6.9 | 261 | 16 | 6.1 | 0.7141 | 0.89 | ( 0.46, 1.70) | 0.88 | ( 0.44, 1.76) | -0.01 | (-0.05, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5869 |
| Low, moderate or high | 1018 | 22 | 2.2 | 1001 | 24 | 2.4 | 0.7218 | 1.11 | ( 0.63, 1.97) | 1.11 | ( 0.62, 2.00) | 0.00 | (-0.01, 0.02) | |
| Very high | 167 | 10 | 6.0 | 162 | 8 | 4.9 | 0.6755 | 0.82 | ( 0.33, 2.04) | 0.82 | ( 0.31, 2.12) | -0.01 | (-0.06, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7722 |
| No | 205 | 4 | 2.0 | 211 | 5 | 2.4 | 0.7693 | 1.21 | ( 0.33, 4.46) | 1.22 | ( 0.32, 4.61) | 0.00 | (-0.02, 0.03) | |
| Yes | 983 | 28 | 2.8 | 960 | 27 | 2.8 | 0.9619 | 0.99 | ( 0.59, 1.66) | 0.99 | ( 0.58, 1.69) | 0.00 | (-0.02, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4779 |
| No | 422 | 20 | 4.7 | 408 | 17 | 4.2 | 0.6894 | 0.88 | ( 0.47, 1.65) | 0.87 | ( 0.45, 1.69) | -0.01 | (-0.03, 0.02) | |
| Yes | 766 | 12 | 1.6 | 763 | 15 | 2.0 | 0.5533 | 1.25 | ( 0.59, 2.66) | 1.26 | ( 0.59, 2.71) | 0.00 | (-0.01, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4237 |
| No | 629 | 17 | 2.7 | 589 | 13 | 2.2 | 0.5771 | 0.82 | ( 0.40, 1.67) | 0.81 | ( 0.39, 1.69) | 0.00 | (-0.02, 0.01) | |
| Yes | 559 | 15 | 2.7 | 582 | 19 | 3.3 | 0.5638 | 1.22 | ( 0.62, 2.37) | 1.22 | ( 0.62, 2.43) | 0.01 | (-0.01, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 62 | 5.2 | 1171 | 46 | 3.9 | 0.1338 | 0.75 | ( 0.52, 1.09) | 0.74 | ( 0.50, 1.10) | -0.01 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.1810 |
| Male | 864 | 35 | 4.1 | 837 | 31 | 3.7 | 0.7108 | 0.91 | ( 0.57, 1.47) | 0.91 | ( 0.56, 1.49) | 0.00 | (-0.02, 0.01) | |
| Female | 324 | 27 | 8.3 | 334 | 15 | 4.5 | 0.0438 | 0.54 | ( 0.29, 0.99) | 0.52 | ( 0.27, 0.99) | -0.04 | (-0.08, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.0804 |
| <65 | 569 | 34 | 6.0 | 547 | 17 | 3.1 | 0.0218 | 0.52 | ( 0.29, 0.92) | 0.50 | ( 0.28, 0.91) | -0.03 | (-0.05, 0.00) | |
| >=65 | 619 | 28 | 4.5 | 624 | 29 | 4.6 | 0.9168 | 1.03 | ( 0.62, 1.71) | 1.03 | ( 0.60, 1.75) | 0.00 | (-0.02, 0.02) | |
| Region | | | | | | | | | | | | | | 0.8571 |
| Europe | 468 | 17 | 3.6 | 434 | 13 | 3.0 | 0.5939 | 0.82 | ( 0.41, 1.68) | 0.82 | ( 0.39, 1.71) | -0.01 | (-0.03, 0.02) | |
| North America | 259 | 10 | 3.9 | 241 | 9 | 3.7 | 0.9410 | 0.97 | ( 0.40, 2.34) | 0.97 | ( 0.39, 2.42) | 0.00 | (-0.03, 0.03) | |
| Latin America | 177 | 10 | 5.6 | 191 | 9 | 4.7 | 0.6846 | 0.83 | ( 0.35, 2.00) | 0.83 | ( 0.33, 2.08) | -0.01 | (-0.05, 0.04) | |
| Africa | 50 | 2 | 4.0 | 54 | 1 | 1.9 | 0.5131 | 0.46 | ( 0.04, 4.95) | 0.45 | ( 0.04, 5.15) | -0.02 | (-0.09, 0.04) | |
| Asia | 234 | 23 | 9.8 | 251 | 14 | 5.6 | 0.0780 | 0.57 | ( 0.30, 1.08) | 0.54 | ( 0.27, 1.08) | -0.04 | (-0.09, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3596 |
| <30 | 554 | 34 | 6.1 | 566 | 22 | 3.9 | 0.0841 | 0.63 | ( 0.38, 1.07) | 0.62 | ( 0.36, 1.07) | -0.02 | (-0.05, 0.00) | |
| >=30 | 634 | 28 | 4.4 | 605 | 24 | 4.0 | 0.6933 | 0.90 | ( 0.53, 1.53) | 0.89 | ( 0.51, 1.56) | 0.00 | (-0.03, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4938 |
| <130 | 379 | 25 | 6.6 | 382 | 16 | 4.2 | 0.1413 | 0.63 | ( 0.34, 1.17) | 0.62 | ( 0.33, 1.18) | -0.02 | (-0.06, 0.01) | |
| >=130 | 809 | 37 | 4.6 | 789 | 30 | 3.8 | 0.4418 | 0.83 | ( 0.52, 1.33) | 0.82 | ( 0.50, 1.35) | -0.01 | (-0.03, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8596 |
| <75 | 500 | 27 | 5.4 | 500 | 18 | 3.6 | 0.1698 | 0.67 | ( 0.37, 1.19) | 0.65 | ( 0.36, 1.20) | -0.02 | (-0.04, 0.01) | |
| 75 to <85 | 427 | 23 | 5.4 | 417 | 18 | 4.3 | 0.4698 | 0.80 | ( 0.44, 1.46) | 0.79 | ( 0.42, 1.49) | -0.01 | (-0.04, 0.02) | |
| >=85 | 261 | 12 | 4.6 | 254 | 10 | 3.9 | 0.7109 | 0.86 | ( 0.38, 1.95) | 0.85 | ( 0.36, 2.00) | -0.01 | (-0.04, 0.03) | |
| History of heart failure | | | | | | | | | | | | | | 0.6156 |
| No | 1048 | 51 | 4.9 | 1031 | 36 | 3.5 | 0.1176 | 0.72 | ( 0.47, 1.09) | 0.71 | ( 0.46, 1.09) | -0.01 | (-0.03, 0.00) | |
| Yes | 140 | 11 | 7.9 | 140 | 10 | 7.1 | 0.8205 | 0.91 | ( 0.40, 2.07) | 0.90 | ( 0.37, 2.20) | -0.01 | (-0.07, 0.05) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2203 |
| <45 | 179 | 12 | 6.7 | 178 | 5 | 2.8 | 0.0840 | 0.42 | ( 0.15, 1.16) | 0.40 | ( 0.14, 1.17) | -0.04 | (-0.08, 0.00) | |
| >=45 | 1009 | 50 | 5.0 | 993 | 41 | 4.1 | 0.3747 | 0.83 | ( 0.56, 1.25) | 0.83 | ( 0.54, 1.26) | -0.01 | (-0.03, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9221 |
| Normal (<30) | 250 | 12 | 4.8 | 257 | 8 | 3.1 | 0.3292 | 0.65 | ( 0.27, 1.56) | 0.64 | ( 0.26, 1.59) | -0.02 | (-0.05, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 38 | 5.6 | 645 | 27 | 4.2 | 0.2256 | 0.74 | ( 0.46, 1.20) | 0.73 | ( 0.44, 1.21) | -0.01 | (-0.04, 0.01) | |
| Macroalbuminuria (>300) | 260 | 12 | 4.6 | 261 | 10 | 3.8 | 0.6564 | 0.83 | ( 0.37, 1.89) | 0.82 | ( 0.35, 1.94) | -0.01 | (-0.04, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7897 |
| Low, moderate or high | 1018 | 56 | 5.5 | 1001 | 40 | 4.0 | 0.1121 | 0.73 | ( 0.49, 1.08) | 0.72 | ( 0.47, 1.08) | -0.02 | (-0.03, 0.00) | |
| Very high | 167 | 6 | 3.6 | 162 | 5 | 3.1 | 0.7984 | 0.86 | ( 0.27, 2.76) | 0.85 | ( 0.26, 2.86) | -0.01 | (-0.04, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5012 |
| No | 205 | 12 | 5.9 | 211 | 7 | 3.3 | 0.2155 | 0.57 | ( 0.23, 1.41) | 0.55 | ( 0.21, 1.43) | -0.03 | (-0.07, 0.01) | |
| Yes | 983 | 50 | 5.1 | 960 | 39 | 4.1 | 0.2804 | 0.80 | ( 0.53, 1.20) | 0.79 | ( 0.51, 1.21) | -0.01 | (-0.03, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4457 |
| No | 422 | 23 | 5.5 | 408 | 20 | 4.9 | 0.7216 | 0.90 | ( 0.50, 1.61) | 0.89 | ( 0.48, 1.65) | -0.01 | (-0.04, 0.02) | |
| Yes | 766 | 39 | 5.1 | 763 | 26 | 3.4 | 0.1027 | 0.67 | ( 0.41, 1.09) | 0.66 | ( 0.40, 1.09) | -0.02 | (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1741 |
| No | 629 | 30 | 4.8 | 589 | 27 | 4.6 | 0.8783 | 0.96 | ( 0.58, 1.60) | 0.96 | ( 0.56, 1.63) | 0.00 | (-0.03, 0.02) | |
| Yes | 559 | 32 | 5.7 | 582 | 19 | 3.3 | 0.0444 | 0.57 | ( 0.33, 0.99) | 0.56 | ( 0.31, 0.99) | -0.02 | (-0.05, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Ketoacidosis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 1 | 0.1 | 1171 | 3 | 0.3 | 0.3100 | 3.04 ( 0.32,29.22) | 3.05 ( 0.32,29.35) | 0.00 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | |
| Male | 864 | 1 | 0.1 | 837 | 3 | 0.4 | | | | | |
| Female | 324 | 0 | 0 | 334 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 1 | 0.2 | 547 | 1 | 0.2 | | | | | |
| >=65 | 619 | 0 | 0 | 624 | 2 | 0.3 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 0 | 0 | 434 | 1 | 0.2 | | | | | |
| North America | 259 | 0 | 0 | 241 | 1 | 0.4 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 1 | 1.9 | | | | | |
| Asia | 234 | 1 | 0.4 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 1 | 0.2 | 566 | 2 | 0.4 | | | | | |
| >=30 | 634 | 0 | 0 | 605 | 1 | 0.2 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 382 | 0 | 0 | | | | | |
| >=130 | 809 | 1 | 0.1 | 789 | 3 | 0.4 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 0 | 0 | 500 | 1 | 0.2 | | | | | |
| 75 to <85 | 427 | 0 | 0 | 417 | 0 | 0 | | | | | |
| >=85 | 261 | 1 | 0.4 | 254 | 2 | 0.8 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 1 | 0.1 | 1031 | 3 | 0.3 | | | | | |
| Yes | 140 | 0 | 0 | 140 | 0 | 0 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 178 | 0 | 0 | | | | | |
| >=45 | 1009 | 1 | 0.1 | 993 | 3 | 0.3 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 0 | 0 | 257 | 1 | 0.4 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 1 | 0.1 | 645 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 1 | 0.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 1 | 0.1 | 1001 | 3 | 0.3 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 0 | 0 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 1 | 0.1 | 960 | 3 | 0.3 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 0 | 0 | 408 | 1 | 0.2 | | | | | |
| Yes | 766 | 1 | 0.1 | 763 | 2 | 0.3 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 1 | 0.2 | 589 | 0 | 0 | | | | | |
| Yes | 559 | 0 | 0 | 582 | 3 | 0.5 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 419 | 35.3 | 1171 | 392 | 33.5 | 0.3591 | 0.95 | ( 0.85, 1.06) | 0.92 | ( 0.78, 1.09) | -0.02 | (-0.06, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.7183 |
| Male | 864 | 299 | 34.6 | 837 | 271 | 32.4 | 0.3302 | 0.94 | ( 0.82, 1.07) | 0.90 | ( 0.74, 1.11) | -0.02 | (-0.07, 0.02) | |
| Female | 324 | 120 | 37.0 | 334 | 121 | 36.2 | 0.8294 | 0.98 | ( 0.80, 1.20) | 0.97 | ( 0.70, 1.33) | -0.01 | (-0.08, 0.07) | |
| Age [years] | | | | | | | | | | | | | | 0.3629 |
| <65 | 569 | 194 | 34.1 | 547 | 187 | 34.2 | 0.9743 | 1.00 | ( 0.85, 1.18) | 1.00 | ( 0.78, 1.29) | 0.00 | (-0.05, 0.06) | |
| >=65 | 619 | 225 | 36.3 | 624 | 205 | 32.9 | 0.1951 | 0.90 | ( 0.78, 1.05) | 0.86 | ( 0.68, 1.08) | -0.03 | (-0.09, 0.02) | |
| Region | | | | | | | | | | | | | | 0.9495 |
| Europe | 468 | 137 | 29.3 | 434 | 123 | 28.3 | 0.7574 | 0.97 | ( 0.79, 1.19) | 0.96 | ( 0.72, 1.28) | -0.01 | (-0.07, 0.05) | |
| North America | 259 | 111 | 42.9 | 241 | 93 | 38.6 | 0.3319 | 0.90 | ( 0.73, 1.11) | 0.84 | ( 0.59, 1.20) | -0.04 | (-0.13, 0.04) | |
| Latin America | 177 | 74 | 41.8 | 191 | 75 | 39.3 | 0.6198 | 0.94 | ( 0.73, 1.20) | 0.90 | ( 0.59, 1.36) | -0.03 | (-0.13, 0.07) | |
| Africa | 50 | 20 | 40.0 | 54 | 18 | 33.3 | 0.4806 | 0.83 | ( 0.50, 1.38) | 0.75 | ( 0.34, 1.67) | -0.07 | (-0.25, 0.12) | |
| Asia | 234 | 77 | 32.9 | 251 | 83 | 33.1 | 0.9698 | 1.00 | ( 0.78, 1.30) | 1.01 | ( 0.69, 1.47) | 0.00 | (-0.08, 0.09) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5280 |
| <30 | 554 | 196 | 35.4 | 566 | 183 | 32.3 | 0.2813 | 0.91 | ( 0.78, 1.08) | 0.87 | ( 0.68, 1.12) | -0.03 | (-0.09, 0.02) | |
| >=30 | 634 | 223 | 35.2 | 605 | 209 | 34.5 | 0.8166 | 0.98 | ( 0.84, 1.14) | 0.97 | ( 0.77, 1.23) | -0.01 | (-0.06, 0.05) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2252 |
| <130 | 379 | 142 | 37.5 | 382 | 123 | 32.2 | 0.1272 | 0.86 | ( 0.71, 1.04) | 0.79 | ( 0.59, 1.07) | -0.05 | (-0.12, 0.01) | |
| >=130 | 809 | 277 | 34.2 | 789 | 269 | 34.1 | 0.9509 | 1.00 | ( 0.87, 1.14) | 0.99 | ( 0.81, 1.22) | 0.00 | (-0.05, 0.05) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8321 |
| <75 | 500 | 209 | 41.8 | 500 | 193 | 38.6 | 0.3021 | 0.92 | ( 0.79, 1.07) | 0.88 | ( 0.68, 1.13) | -0.03 | (-0.09, 0.03) | |
| 75 to <85 | 427 | 132 | 30.9 | 417 | 122 | 29.3 | 0.5998 | 0.95 | ( 0.77, 1.16) | 0.92 | ( 0.69, 1.24) | -0.02 | (-0.08, 0.05) | |
| >=85 | 261 | 78 | 29.9 | 254 | 77 | 30.3 | 0.9153 | 1.01 | ( 0.78, 1.32) | 1.02 | ( 0.70, 1.49) | 0.00 | (-0.07, 0.08) | |
| History of heart failure | | | | | | | | | | | | | | 0.9350 |
| No | 1048 | 368 | 35.1 | 1031 | 343 | 33.3 | 0.3750 | 0.95 | ( 0.84, 1.07) | 0.92 | ( 0.77, 1.10) | -0.02 | (-0.06, 0.02) | |
| Yes | 140 | 51 | 36.4 | 140 | 49 | 35.0 | 0.8030 | 0.96 | ( 0.70, 1.32) | 0.94 | ( 0.58, 1.53) | -0.01 | (-0.13, 0.10) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4989 |
| <45 | 179 | 78 | 43.6 | 178 | 68 | 38.2 | 0.3018 | 0.88 | ( 0.68, 1.13) | 0.80 | ( 0.52, 1.22) | -0.05 | (-0.16, 0.05) | |
| >=45 | 1009 | 341 | 33.8 | 993 | 324 | 32.6 | 0.5792 | 0.97 | ( 0.85, 1.09) | 0.95 | ( 0.79, 1.14) | -0.01 | (-0.05, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8051 |
| Normal (<30) | 250 | 93 | 37.2 | 257 | 90 | 35.0 | 0.6093 | 0.94 | ( 0.75, 1.19) | 0.91 | ( 0.63, 1.31) | -0.02 | (-0.11, 0.06) | |
| Microalbuminuria (30 to <=300) | 675 | 221 | 32.7 | 645 | 204 | 31.6 | 0.6653 | 0.97 | ( 0.83, 1.13) | 0.95 | ( 0.75, 1.20) | -0.01 | (-0.06, 0.04) | |
| Macroalbuminuria (>300) | 260 | 105 | 40.4 | 261 | 93 | 35.6 | 0.2638 | 0.88 | ( 0.71, 1.10) | 0.82 | ( 0.57, 1.16) | -0.05 | (-0.13, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0356 |
| Low, moderate or high | 1018 | 336 | 33.0 | 1001 | 328 | 32.8 | 0.9091 | 0.99 | ( 0.88, 1.12) | 0.99 | ( 0.82, 1.19) | 0.00 | (-0.04, 0.04) | |
| Very high | 167 | 83 | 49.7 | 162 | 59 | 36.4 | 0.0150 | 0.73 | ( 0.57, 0.94) | 0.58 | ( 0.37, 0.90) | -0.13 | (-0.24,-0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2021 |
| No | 205 | 64 | 31.2 | 211 | 52 | 24.6 | 0.1349 | 0.79 | ( 0.58, 1.08) | 0.72 | ( 0.47, 1.11) | -0.07 | (-0.15, 0.02) | |
| Yes | 983 | 355 | 36.1 | 960 | 340 | 35.4 | 0.7485 | 0.98 | ( 0.87, 1.10) | 0.97 | ( 0.81, 1.17) | -0.01 | (-0.05, 0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.0360 |
| No | 422 | 145 | 34.4 | 408 | 111 | 27.2 | 0.0257 | 0.79 | ( 0.64, 0.97) | 0.71 | ( 0.53, 0.96) | -0.07 | (-0.13,-0.01) | |
| Yes | 766 | 274 | 35.8 | 763 | 281 | 36.8 | 0.6671 | 1.03 | ( 0.90, 1.18) | 1.05 | ( 0.85, 1.29) | 0.01 | (-0.04, 0.06) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2104 |
| No | 629 | 212 | 33.7 | 589 | 174 | 29.5 | 0.1187 | 0.88 | ( 0.74, 1.03) | 0.82 | ( 0.65, 1.05) | -0.04 | (-0.09, 0.01) | |
| Yes | 559 | 207 | 37.0 | 582 | 218 | 37.5 | 0.8815 | 1.01 | ( 0.87, 1.18) | 1.02 | ( 0.80, 1.29) | 0.00 | (-0.05, 0.06) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 262 | 22.1 | 1171 | 260 | 22.2 | 0.9304 | 1.01 | ( 0.87, 1.17) | 1.01 | ( 0.83, 1.23) | 0.00 | (-0.03, 0.03) | |
| Sex | | | | | | | | | | | | | | 0.2212 |
| Male | 864 | 108 | 12.5 | 837 | 115 | 13.7 | 0.4489 | 1.10 | ( 0.86, 1.40) | 1.11 | ( 0.84, 1.48) | 0.01 | (-0.02, 0.04) | |
| Female | 324 | 154 | 47.5 | 334 | 145 | 43.4 | 0.2889 | 0.91 | ( 0.77, 1.08) | 0.85 | ( 0.62, 1.15) | -0.04 | (-0.12, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.5920 |
| <65 | 569 | 105 | 18.5 | 547 | 96 | 17.6 | 0.6947 | 0.95 | ( 0.74, 1.22) | 0.94 | ( 0.69, 1.28) | -0.01 | (-0.05, 0.04) | |
| >=65 | 619 | 157 | 25.4 | 624 | 164 | 26.3 | 0.7114 | 1.04 | ( 0.86, 1.25) | 1.05 | ( 0.81, 1.35) | 0.01 | (-0.04, 0.06) | |
| Region | | | | | | | | | | | | | | 0.4564 |
| Europe | 468 | 96 | 20.5 | 434 | 83 | 19.1 | 0.6014 | 0.93 | ( 0.72, 1.21) | 0.92 | ( 0.66, 1.27) | -0.01 | (-0.07, 0.04) | |
| North America | 259 | 53 | 20.5 | 241 | 51 | 21.2 | 0.8475 | 1.03 | ( 0.73, 1.46) | 1.04 | ( 0.68, 1.61) | 0.01 | (-0.06, 0.08) | |
| Latin America | 177 | 48 | 27.1 | 191 | 52 | 27.2 | 0.9817 | 1.00 | ( 0.72, 1.40) | 1.01 | ( 0.63, 1.59) | 0.00 | (-0.09, 0.09) | |
| Africa | 50 | 8 | 16.0 | 54 | 17 | 31.5 | 0.0649 | 1.97 | ( 0.93, 4.15) | 2.41 | ( 0.93, 6.23) | 0.15 | (-0.01, 0.32) | |
| Asia | 234 | 57 | 24.4 | 251 | 57 | 22.7 | 0.6685 | 0.93 | ( 0.68, 1.29) | 0.91 | ( 0.60, 1.39) | -0.02 | (-0.09, 0.06) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3996 |
| <30 | 554 | 128 | 23.1 | 566 | 123 | 21.7 | 0.5816 | 0.94 | ( 0.76, 1.17) | 0.92 | ( 0.70, 1.22) | -0.01 | (-0.06, 0.04) | |
| >=30 | 634 | 134 | 21.1 | 605 | 137 | 22.6 | 0.5207 | 1.07 | ( 0.87, 1.32) | 1.09 | ( 0.83, 1.43) | 0.02 | (-0.03, 0.06) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0314 |
| <130 | 379 | 91 | 24.0 | 382 | 72 | 18.8 | 0.0826 | 0.78 | ( 0.60, 1.03) | 0.74 | ( 0.52, 1.04) | -0.05 | (-0.11, 0.01) | |
| >=130 | 809 | 171 | 21.1 | 789 | 188 | 23.8 | 0.1976 | 1.13 | ( 0.94, 1.35) | 1.17 | ( 0.92, 1.48) | 0.03 | (-0.01, 0.07) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8002 |
| <75 | 500 | 109 | 21.8 | 500 | 115 | 23.0 | 0.6490 | 1.06 | ( 0.84, 1.33) | 1.07 | ( 0.80, 1.44) | 0.01 | (-0.04, 0.06) | |
| 75 to <85 | 427 | 100 | 23.4 | 417 | 92 | 22.1 | 0.6383 | 0.94 | ( 0.73, 1.21) | 0.93 | ( 0.67, 1.28) | -0.01 | (-0.07, 0.04) | |
| >=85 | 261 | 53 | 20.3 | 254 | 53 | 20.9 | 0.8752 | 1.03 | ( 0.73, 1.44) | 1.03 | ( 0.68, 1.59) | 0.01 | (-0.06, 0.08) | |
| History of heart failure | | | | | | | | | | | | | | 0.9735 |
| No | 1048 | 228 | 21.8 | 1031 | 226 | 21.9 | 0.9276 | 1.01 | ( 0.86, 1.19) | 1.01 | ( 0.82, 1.24) | 0.00 | (-0.03, 0.04) | |
| Yes | 140 | 34 | 24.3 | 140 | 34 | 24.3 | 1.0000 | 1.00 | ( 0.66, 1.51) | 1.00 | ( 0.58, 1.73) | 0.00 | (-0.10, 0.10) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7010 |
| <45 | 179 | 49 | 27.4 | 178 | 52 | 29.2 | 0.6997 | 1.07 | ( 0.77, 1.49) | 1.09 | ( 0.69, 1.74) | 0.02 | (-0.08, 0.11) | |
| >=45 | 1009 | 213 | 21.1 | 993 | 208 | 20.9 | 0.9285 | 0.99 | ( 0.84, 1.18) | 0.99 | ( 0.80, 1.23) | 0.00 | (-0.04, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6744 |
| Normal (<30) | 250 | 57 | 22.8 | 257 | 62 | 24.1 | 0.7250 | 1.06 | ( 0.77, 1.45) | 1.08 | ( 0.71, 1.62) | 0.01 | (-0.06, 0.09) | |
| Microalbuminuria (30 to <=300) | 675 | 148 | 21.9 | 645 | 132 | 20.5 | 0.5164 | 0.93 | ( 0.76, 1.15) | 0.92 | ( 0.70, 1.19) | -0.01 | (-0.06, 0.03) | |
| Macroalbuminuria (>300) | 260 | 57 | 21.9 | 261 | 62 | 23.8 | 0.6185 | 1.08 | ( 0.79, 1.49) | 1.11 | ( 0.74, 1.67) | 0.02 | (-0.05, 0.09) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3081 |
| Low, moderate or high | 1018 | 221 | 21.7 | 1001 | 209 | 20.9 | 0.6487 | 0.96 | ( 0.81, 1.14) | 0.95 | ( 0.77, 1.18) | -0.01 | (-0.04, 0.03) | |
| Very high | 167 | 41 | 24.6 | 162 | 47 | 29.0 | 0.3607 | 1.18 | ( 0.83, 1.69) | 1.26 | ( 0.77, 2.05) | 0.04 | (-0.05, 0.14) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7839 |
| No | 205 | 51 | 24.9 | 211 | 55 | 26.1 | 0.7810 | 1.05 | ( 0.75, 1.46) | 1.06 | ( 0.68, 1.66) | 0.01 | (-0.07, 0.10) | |
| Yes | 983 | 211 | 21.5 | 960 | 205 | 21.4 | 0.9526 | 0.99 | ( 0.84, 1.18) | 0.99 | ( 0.80, 1.23) | 0.00 | (-0.04, 0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2874 |
| No | 422 | 107 | 25.4 | 408 | 94 | 23.0 | 0.4361 | 0.91 | ( 0.71, 1.16) | 0.88 | ( 0.64, 1.21) | -0.02 | (-0.08, 0.04) | |
| Yes | 766 | 155 | 20.2 | 763 | 166 | 21.8 | 0.4652 | 1.08 | ( 0.89, 1.31) | 1.10 | ( 0.86, 1.40) | 0.02 | (-0.03, 0.06) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5329 |
| No | 629 | 124 | 19.7 | 589 | 110 | 18.7 | 0.6458 | 0.95 | ( 0.75, 1.19) | 0.94 | ( 0.70, 1.24) | -0.01 | (-0.05, 0.03) | |
| Yes | 559 | 138 | 24.7 | 582 | 150 | 25.8 | 0.6728 | 1.04 | ( 0.85, 1.28) | 1.06 | ( 0.81, 1.38) | 0.01 | (-0.04, 0.06) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pylenophritis or Urosepsis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 20 | 1.7 | 1171 | 14 | 1.2 | 0.3201 | 0.71 | ( 0.36, 1.40) | 0.71 | ( 0.36, 1.41) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.7456 |
| Male | 864 | 10 | 1.2 | 837 | 6 | 0.7 | 0.3467 | 0.62 | ( 0.23, 1.70) | 0.62 | ( 0.22, 1.70) | 0.00 | (-0.01, 0.00) | |
| Female | 324 | 10 | 3.1 | 334 | 8 | 2.4 | 0.5868 | 0.78 | ( 0.31, 1.94) | 0.77 | ( 0.30, 1.98) | -0.01 | (-0.03, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.2073 |
| <65 | 569 | 7 | 1.2 | 547 | 2 | 0.4 | 0.1064 | 0.30 | ( 0.06, 1.42) | 0.29 | ( 0.06, 1.42) | -0.01 | (-0.02, 0.00) | |
| >=65 | 619 | 13 | 2.1 | 624 | 12 | 1.9 | 0.8240 | 0.92 | ( 0.42, 1.99) | 0.91 | ( 0.41, 2.02) | 0.00 | (-0.02, 0.01) | |
| Region | | | | | | | | | | | | | | 0.8954 |
| Europe | 468 | 12 | 2.6 | 434 | 6 | 1.4 | 0.2048 | 0.54 | ( 0.20, 1.42) | 0.53 | ( 0.20, 1.43) | -0.01 | (-0.03, 0.01) | |
| North America | 259 | 3 | 1.2 | 241 | 2 | 0.8 | 0.7123 | 0.72 | ( 0.12, 4.25) | 0.71 | ( 0.12, 4.31) | 0.00 | (-0.02, 0.01) | |
| Latin America | 177 | 1 | 0.6 | 191 | 2 | 1.0 | 0.6073 | 1.85 | ( 0.17,20.26) | 1.86 | ( 0.17,20.72) | 0.00 | (-0.01, 0.02) | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | 0.9697 | 0.93 | ( 0.02,45.87) | 0.93 | ( 0.02,47.58) | 0.00 | (-0.04, 0.04) | |
| Asia | 234 | 4 | 1.7 | 251 | 4 | 1.6 | 0.9203 | 0.93 | ( 0.24, 3.69) | 0.93 | ( 0.23, 3.77) | 0.00 | (-0.02, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8486 |
| <30 | 554 | 9 | 1.6 | 566 | 7 | 1.2 | 0.5845 | 0.76 | ( 0.29, 2.03) | 0.76 | ( 0.28, 2.05) | 0.00 | (-0.02, 0.01) | |
| >=30 | 634 | 11 | 1.7 | 605 | 7 | 1.2 | 0.3954 | 0.67 | ( 0.26, 1.71) | 0.66 | ( 0.26, 1.72) | -0.01 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4289 |
| <130 | 379 | 5 | 1.3 | 382 | 2 | 0.5 | 0.2503 | 0.40 | ( 0.08, 2.03) | 0.39 | ( 0.08, 2.04) | -0.01 | (-0.02, 0.01) | |
| >=130 | 809 | 15 | 1.9 | 789 | 12 | 1.5 | 0.6053 | 0.82 | ( 0.39, 1.74) | 0.82 | ( 0.38, 1.76) | 0.00 | (-0.02, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7611 |
| <75 | 500 | 6 | 1.2 | 500 | 6 | 1.2 | 1.0000 | 1.00 | ( 0.32, 3.08) | 1.00 | ( 0.32, 3.12) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 427 | 7 | 1.6 | 417 | 4 | 1.0 | 0.3838 | 0.59 | ( 0.17, 1.98) | 0.58 | ( 0.17, 2.00) | -0.01 | (-0.02, 0.01) | |
| >=85 | 261 | 7 | 2.7 | 254 | 4 | 1.6 | 0.3849 | 0.59 | ( 0.17, 1.98) | 0.58 | ( 0.17, 2.01) | -0.01 | (-0.04, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.1739 |
| No | 1048 | 16 | 1.5 | 1031 | 14 | 1.4 | 0.7469 | 0.89 | ( 0.44, 1.81) | 0.89 | ( 0.43, 1.83) | 0.00 | (-0.01, 0.01) | |
| Yes | 140 | 4 | 2.9 | 140 | 0 | 0 | 0.0711 | 0.11 | (<0.01, 2.04) | 0.11 | (<0.01, 2.02) | -0.03 | (-0.06, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pylenophritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2882 |
| <45 | 179 | 6 | 3.4 | 178 | 2 | 1.1 | 0.1549 | 0.34 | ( 0.07, 1.64) | 0.33 | ( 0.07, 1.65) | -0.02 | (-0.05, 0.01) | |
| >=45 | 1009 | 14 | 1.4 | 993 | 12 | 1.2 | 0.7235 | 0.87 | ( 0.40, 1.87) | 0.87 | ( 0.40, 1.89) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1320 |
| Normal (<30) | 250 | 7 | 2.8 | 257 | 1 | 0.4 | 0.0294 | 0.14 | ( 0.02, 1.12) | 0.14 | ( 0.02, 1.11) | -0.02 | (-0.05, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 12 | 1.8 | 645 | 10 | 1.6 | 0.7470 | 0.87 | ( 0.38, 2.00) | 0.87 | ( 0.37, 2.03) | 0.00 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 260 | 1 | 0.4 | 261 | 3 | 1.1 | 0.3173 | 2.99 | ( 0.31,28.54) | 3.01 | ( 0.31,29.14) | 0.01 | (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.6163 |
| Low, moderate or high | 1018 | 17 | 1.7 | 1001 | 11 | 1.1 | 0.2726 | 0.66 | ( 0.31, 1.40) | 0.65 | ( 0.30, 1.40) | -0.01 | (-0.02, 0.00) | |
| Very high | 167 | 3 | 1.8 | 162 | 3 | 1.9 | 0.9700 | 1.03 | ( 0.21, 5.03) | 1.03 | ( 0.21, 5.19) | 0.00 | (-0.03, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9110 |
| No | 205 | 3 | 1.5 | 211 | 2 | 0.9 | 0.6295 | 0.65 | ( 0.11, 3.84) | 0.64 | ( 0.11, 3.90) | -0.01 | (-0.03, 0.02) | |
| Yes | 983 | 17 | 1.7 | 960 | 12 | 1.3 | 0.3836 | 0.72 | ( 0.35, 1.51) | 0.72 | ( 0.34, 1.51) | 0.00 | (-0.02, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9346 |
| No | 422 | 9 | 2.1 | 408 | 6 | 1.5 | 0.4741 | 0.69 | ( 0.25, 1.92) | 0.68 | ( 0.24, 1.94) | -0.01 | (-0.02, 0.01) | |
| Yes | 766 | 11 | 1.4 | 763 | 8 | 1.0 | 0.4940 | 0.73 | ( 0.30, 1.81) | 0.73 | ( 0.29, 1.82) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4637 |
| No | 629 | 8 | 1.3 | 589 | 7 | 1.2 | 0.8951 | 0.93 | ( 0.34, 2.56) | 0.93 | ( 0.34, 2.59) | 0.00 | (-0.01, 0.01) | |
| Yes | 559 | 12 | 2.1 | 582 | 7 | 1.2 | 0.2129 | 0.56 | ( 0.22, 1.41) | 0.55 | ( 0.22, 1.42) | -0.01 | (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 22 | 1.9 | 1171 | 57 | 4.9 | <0.0001 | 2.63 | ( 1.62, 4.27) | 2.71 | ( 1.65, 4.47) | 0.03 | ( 0.02, 0.04) | |
| Sex | | | | | | | | | | | | | | 0.2538 |
| Male | 864 | 15 | 1.7 | 837 | 30 | 3.6 | 0.0176 | 2.06 | ( 1.12, 3.81) | 2.10 | ( 1.12, 3.94) | 0.02 | ( 0.00, 0.03) | |
| Female | 324 | 7 | 2.2 | 334 | 27 | 8.1 | 0.0006 | 3.74 | ( 1.65, 8.47) | 3.98 | ( 1.71, 9.28) | 0.06 | ( 0.03, 0.09) | |
| Age [years] | | | | | | | | | | | | | | 0.4615 |
| <65 | 569 | 11 | 1.9 | 547 | 33 | 6.0 | 0.0004 | 3.12 | ( 1.59, 6.11) | 3.26 | ( 1.63, 6.51) | 0.04 | ( 0.02, 0.06) | |
| >=65 | 619 | 11 | 1.8 | 624 | 24 | 3.8 | 0.0275 | 2.16 | ( 1.07, 4.38) | 2.21 | ( 1.07, 4.55) | 0.02 | ( 0.00, 0.04) | |
| Region | | | | | | | | | | | | | | 0.7709 |
| Europe | 468 | 10 | 2.1 | 434 | 18 | 4.1 | 0.0819 | 1.94 | ( 0.91, 4.16) | 1.98 | ( 0.90, 4.34) | 0.02 | ( 0.00, 0.04) | |
| North America | 259 | 6 | 2.3 | 241 | 19 | 7.9 | 0.0043 | 3.40 | ( 1.38, 8.38) | 3.61 | ( 1.42, 9.20) | 0.06 | ( 0.02, 0.09) | |
| Latin America | 177 | 3 | 1.7 | 191 | 6 | 3.1 | 0.3694 | 1.85 | ( 0.47, 7.30) | 1.88 | ( 0.46, 7.64) | 0.01 | (-0.02, 0.05) | |
| Africa | 50 | 1 | 2.0 | 54 | 5 | 9.3 | 0.1127 | 4.63 | ( 0.56,38.27) | 5.00 | ( 0.56,44.38) | 0.07 | (-0.01, 0.16) | |
| Asia | 234 | 2 | 0.9 | 251 | 9 | 3.6 | 0.0435 | 4.20 | ( 0.92,19.22) | 4.31 | ( 0.92,20.18) | 0.03 | ( 0.00, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4936 |
| <30 | 554 | 6 | 1.1 | 566 | 21 | 3.7 | 0.0042 | 3.43 | ( 1.39, 8.42) | 3.52 | ( 1.41, 8.79) | 0.03 | ( 0.01, 0.04) | |
| >=30 | 634 | 16 | 2.5 | 605 | 36 | 6.0 | 0.0026 | 2.36 | ( 1.32, 4.20) | 2.44 | ( 1.34, 4.45) | 0.03 | ( 0.01, 0.06) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3863 |
| <130 | 379 | 5 | 1.3 | 382 | 19 | 5.0 | 0.0039 | 3.77 | ( 1.42, 9.99) | 3.92 | ( 1.45,10.60) | 0.04 | ( 0.01, 0.06) | |
| >=130 | 809 | 17 | 2.1 | 789 | 38 | 4.8 | 0.0029 | 2.29 | ( 1.30, 4.03) | 2.36 | ( 1.32, 4.21) | 0.03 | ( 0.01, 0.05) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9592 |
| <75 | 500 | 8 | 1.6 | 500 | 23 | 4.6 | 0.0062 | 2.88 | ( 1.30, 6.37) | 2.97 | ( 1.31, 6.69) | 0.03 | ( 0.01, 0.05) | |
| 75 to <85 | 427 | 10 | 2.3 | 417 | 24 | 5.8 | 0.0117 | 2.46 | ( 1.19, 5.08) | 2.55 | ( 1.20, 5.39) | 0.03 | ( 0.01, 0.06) | |
| >=85 | 261 | 4 | 1.5 | 254 | 10 | 3.9 | 0.0934 | 2.57 | ( 0.82, 8.09) | 2.63 | ( 0.82, 8.51) | 0.02 | ( 0.00, 0.05) | |
| History of heart failure | | | | | | | | | | | | | | 0.5653 |
| No | 1048 | 20 | 1.9 | 1031 | 49 | 4.8 | 0.0003 | 2.49 | ( 1.49, 4.16) | 2.56 | ( 1.51, 4.35) | 0.03 | ( 0.01, 0.04) | |
| Yes | 140 | 2 | 1.4 | 140 | 8 | 5.7 | 0.0533 | 4.00 | ( 0.86,18.50) | 4.18 | ( 0.87,20.06) | 0.04 | ( 0.00, 0.09) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5105 |
| <45 | 179 | 3 | 1.7 | 178 | 5 | 2.8 | 0.4696 | 1.68 | ( 0.41, 6.91) | 1.70 | ( 0.40, 7.20) | 0.01 | (-0.02, 0.04) | |
| >=45 | 1009 | 19 | 1.9 | 993 | 52 | 5.2 | <0.0001 | 2.78 | ( 1.66, 4.67) | 2.88 | ( 1.69, 4.91) | 0.03 | ( 0.02, 0.05) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6391 |
| Normal (<30) | 250 | 5 | 2.0 | 257 | 14 | 5.4 | 0.0410 | 2.72 | (<1.00, 7.45) | 2.82 | ( 1.00, 7.96) | 0.03 | ( 0.00, 0.07) | |
| Microalbuminuria (30 to <=300) | 675 | 13 | 1.9 | 645 | 27 | 4.2 | 0.0166 | 2.17 | ( 1.13, 4.18) | 2.22 | ( 1.14, 4.35) | 0.02 | ( 0.00, 0.04) | |
| Macroalbuminuria (>300) | 260 | 4 | 1.5 | 261 | 16 | 6.1 | 0.0064 | 3.98 | ( 1.35,11.76) | 4.18 | ( 1.38,12.68) | 0.05 | ( 0.01, 0.08) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5303 |
| Low, moderate or high | 1018 | 19 | 1.9 | 1001 | 52 | 5.2 | <0.0001 | 2.78 | ( 1.66, 4.67) | 2.88 | ( 1.69, 4.91) | 0.03 | ( 0.02, 0.05) | |
| Very high | 167 | 3 | 1.8 | 162 | 5 | 3.1 | 0.4476 | 1.72 | ( 0.42, 7.07) | 1.74 | ( 0.41, 7.41) | 0.01 | (-0.02, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.8136 |
| No | 205 | 3 | 1.5 | 211 | 7 | 3.3 | 0.2171 | 2.27 | ( 0.59, 8.65) | 2.31 | ( 0.59, 9.06) | 0.02 | (-0.01, 0.05) | |
| Yes | 983 | 19 | 1.9 | 960 | 50 | 5.2 | <0.0001 | 2.69 | ( 1.60, 4.54) | 2.79 | ( 1.63, 4.76) | 0.03 | ( 0.02, 0.05) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6604 |
| No | 422 | 7 | 1.7 | 408 | 15 | 3.7 | 0.0704 | 2.22 | ( 0.91, 5.38) | 2.26 | ( 0.91, 5.61) | 0.02 | ( 0.00, 0.04) | |
| Yes | 766 | 15 | 2.0 | 763 | 42 | 5.5 | 0.0003 | 2.81 | ( 1.57, 5.03) | 2.92 | ( 1.60, 5.31) | 0.04 | ( 0.02, 0.05) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4123 |
| No | 629 | 8 | 1.3 | 589 | 25 | 4.2 | 0.0014 | 3.34 | ( 1.52, 7.34) | 3.44 | ( 1.54, 7.69) | 0.03 | ( 0.01, 0.05) | |
| Yes | 559 | 14 | 2.5 | 582 | 32 | 5.5 | 0.0102 | 2.20 | ( 1.18, 4.07) | 2.26 | ( 1.20, 4.29) | 0.03 | ( 0.01, 0.05) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 60 | 5.1 | 1171 | 58 | 5.0 | 0.9135 | 0.98 | ( 0.69, 1.39) | 0.98 | ( 0.68, 1.42) | 0.00 | (-0.02, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.2500 |
| Male | 864 | 31 | 3.6 | 837 | 35 | 4.2 | 0.5262 | 1.17 | ( 0.73, 1.87) | 1.17 | ( 0.72, 1.92) | 0.01 | (-0.01, 0.02) | |
| Female | 324 | 29 | 9.0 | 334 | 23 | 6.9 | 0.3264 | 0.77 | ( 0.45, 1.30) | 0.75 | ( 0.43, 1.33) | -0.02 | (-0.06, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.6372 |
| <65 | 569 | 27 | 4.7 | 547 | 23 | 4.2 | 0.6626 | 0.89 | ( 0.51, 1.53) | 0.88 | ( 0.50, 1.56) | -0.01 | (-0.03, 0.02) | |
| >=65 | 619 | 33 | 5.3 | 624 | 35 | 5.6 | 0.8295 | 1.05 | ( 0.66, 1.67) | 1.06 | ( 0.65, 1.72) | 0.00 | (-0.02, 0.03) | |
| Region | | | | | | | | | | | | | | 0.3616 |
| Europe | 468 | 18 | 3.8 | 434 | 16 | 3.7 | 0.9000 | 0.96 | ( 0.50, 1.86) | 0.96 | ( 0.48, 1.90) | 0.00 | (-0.03, 0.02) | |
| North America | 259 | 20 | 7.7 | 241 | 18 | 7.5 | 0.9150 | 0.97 | ( 0.52, 1.78) | 0.96 | ( 0.50, 1.87) | 0.00 | (-0.05, 0.04) | |
| Latin America | 177 | 12 | 6.8 | 191 | 7 | 3.7 | 0.1773 | 0.54 | ( 0.22, 1.34) | 0.52 | ( 0.20, 1.36) | -0.03 | (-0.08, 0.01) | |
| Africa | 50 | 2 | 4.0 | 54 | 1 | 1.9 | 0.5131 | 0.46 | ( 0.04, 4.95) | 0.45 | ( 0.04, 5.15) | -0.02 | (-0.09, 0.04) | |
| Asia | 234 | 8 | 3.4 | 251 | 16 | 6.4 | 0.1337 | 1.86 | ( 0.81, 4.28) | 1.92 | ( 0.81, 4.58) | 0.03 | (-0.01, 0.07) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0382 |
| <30 | 554 | 34 | 6.1 | 566 | 23 | 4.1 | 0.1144 | 0.66 | ( 0.40, 1.11) | 0.65 | ( 0.38, 1.11) | -0.02 | (-0.05, 0.01) | |
| >=30 | 634 | 26 | 4.1 | 605 | 35 | 5.8 | 0.1708 | 1.41 | ( 0.86, 2.31) | 1.44 | ( 0.85, 2.42) | 0.02 | (-0.01, 0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5784 |
| <130 | 379 | 21 | 5.5 | 382 | 18 | 4.7 | 0.6041 | 0.85 | ( 0.46, 1.57) | 0.84 | ( 0.44, 1.61) | -0.01 | (-0.04, 0.02) | |
| >=130 | 809 | 39 | 4.8 | 789 | 40 | 5.1 | 0.8185 | 1.05 | ( 0.68, 1.62) | 1.05 | ( 0.67, 1.66) | 0.00 | (-0.02, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5705 |
| <75 | 500 | 28 | 5.6 | 500 | 31 | 6.2 | 0.6872 | 1.11 | ( 0.67, 1.82) | 1.11 | ( 0.66, 1.89) | 0.01 | (-0.02, 0.04) | |
| 75 to <85 | 427 | 21 | 4.9 | 417 | 15 | 3.6 | 0.3424 | 0.73 | ( 0.38, 1.40) | 0.72 | ( 0.37, 1.42) | -0.01 | (-0.04, 0.01) | |
| >=85 | 261 | 11 | 4.2 | 254 | 12 | 4.7 | 0.7794 | 1.12 | ( 0.50, 2.49) | 1.13 | ( 0.49, 2.60) | 0.01 | (-0.03, 0.04) | |
| History of heart failure | | | | | | | | | | | | | | 0.4465 |
| No | 1048 | 50 | 4.8 | 1031 | 51 | 4.9 | 0.8522 | 1.04 | ( 0.71, 1.52) | 1.04 | ( 0.70, 1.55) | 0.00 | (-0.02, 0.02) | |
| Yes | 140 | 10 | 7.1 | 140 | 7 | 5.0 | 0.4528 | 0.70 | ( 0.27, 1.79) | 0.68 | ( 0.25, 1.85) | -0.02 | (-0.08, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2184 |
| <45 | 179 | 10 | 5.6 | 178 | 15 | 8.4 | 0.2930 | 1.51 | ( 0.70, 3.27) | 1.56 | ( 0.68, 3.56) | 0.03 | (-0.02, 0.08) | |
| >=45 | 1009 | 50 | 5.0 | 993 | 43 | 4.3 | 0.5064 | 0.87 | ( 0.59, 1.30) | 0.87 | ( 0.57, 1.32) | -0.01 | (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2608 |
| Normal (<30) | 250 | 17 | 6.8 | 257 | 16 | 6.2 | 0.7933 | 0.92 | ( 0.47, 1.77) | 0.91 | ( 0.45, 1.84) | -0.01 | (-0.05, 0.04) | |
| Microalbuminuria (30 to <=300) | 675 | 33 | 4.9 | 645 | 25 | 3.9 | 0.3694 | 0.79 | ( 0.48, 1.32) | 0.78 | ( 0.46, 1.33) | -0.01 | (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 260 | 10 | 3.8 | 261 | 17 | 6.5 | 0.1697 | 1.69 | ( 0.79, 3.63) | 1.74 | ( 0.78, 3.88) | 0.03 | (-0.01, 0.06) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3997 |
| Low, moderate or high | 1018 | 50 | 4.9 | 1001 | 45 | 4.5 | 0.6589 | 0.92 | ( 0.62, 1.36) | 0.91 | ( 0.60, 1.38) | 0.00 | (-0.02, 0.01) | |
| Very high | 167 | 10 | 6.0 | 162 | 13 | 8.0 | 0.4689 | 1.34 | ( 0.60, 2.97) | 1.37 | ( 0.58, 3.22) | 0.02 | (-0.03, 0.08) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9805 |
| No | 205 | 10 | 4.9 | 211 | 10 | 4.7 | 0.9473 | 0.97 | ( 0.41, 2.28) | 0.97 | ( 0.40, 2.38) | 0.00 | (-0.04, 0.04) | |
| Yes | 983 | 50 | 5.1 | 960 | 48 | 5.0 | 0.9306 | 0.98 | ( 0.67, 1.45) | 0.98 | ( 0.65, 1.47) | 0.00 | (-0.02, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6717 |
| No | 422 | 22 | 5.2 | 408 | 23 | 5.6 | 0.7874 | 1.08 | ( 0.61, 1.91) | 1.09 | ( 0.60, 1.98) | 0.00 | (-0.03, 0.04) | |
| Yes | 766 | 38 | 5.0 | 763 | 35 | 4.6 | 0.7319 | 0.92 | ( 0.59, 1.45) | 0.92 | ( 0.58, 1.47) | 0.00 | (-0.03, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4097 |
| No | 629 | 37 | 5.9 | 589 | 30 | 5.1 | 0.5462 | 0.87 | ( 0.54, 1.38) | 0.86 | ( 0.52, 1.41) | -0.01 | (-0.03, 0.02) | |
| Yes | 559 | 23 | 4.1 | 582 | 28 | 4.8 | 0.5692 | 1.17 | ( 0.68, 2.00) | 1.18 | ( 0.67, 2.07) | 0.01 | (-0.02, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
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MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 73 | 6.1 | 1171 | 76 | 6.5 | 0.7302 | 1.06 | ( 0.77, 1.44) | 1.06 | ( 0.76, 1.48) | 0.00 | (-0.02, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.6626 |
| Male | 864 | 55 | 6.4 | 837 | 54 | 6.5 | 0.9424 | 1.01 | ( 0.70, 1.46) | 1.01 | ( 0.69, 1.50) | 0.00 | (-0.02, 0.02) | |
| Female | 324 | 18 | 5.6 | 334 | 22 | 6.6 | 0.5799 | 1.19 | ( 0.65, 2.17) | 1.20 | ( 0.63, 2.28) | 0.01 | (-0.03, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.3408 |
| <65 | 569 | 24 | 4.2 | 547 | 19 | 3.5 | 0.5183 | 0.82 | ( 0.46, 1.49) | 0.82 | ( 0.44, 1.51) | -0.01 | (-0.03, 0.02) | |
| >=65 | 619 | 49 | 7.9 | 624 | 57 | 9.1 | 0.4418 | 1.15 | ( 0.80, 1.66) | 1.17 | ( 0.78, 1.74) | 0.01 | (-0.02, 0.04) | |
| Region | | | | | | | | | | | | | | 0.3056 |
| Europe | 468 | 26 | 5.6 | 434 | 29 | 6.7 | 0.4799 | 1.20 | ( 0.72, 2.01) | 1.22 | ( 0.70, 2.10) | 0.01 | (-0.02, 0.04) | |
| North America | 259 | 32 | 12.4 | 241 | 21 | 8.7 | 0.1863 | 0.71 | ( 0.42, 1.19) | 0.68 | ( 0.38, 1.21) | -0.04 | (-0.09, 0.02) | |
| Latin America | 177 | 6 | 3.4 | 191 | 12 | 6.3 | 0.1986 | 1.85 | ( 0.71, 4.83) | 1.91 | ( 0.70, 5.20) | 0.03 | (-0.01, 0.07) | |
| Africa | 50 | 3 | 6.0 | 54 | 3 | 5.6 | 0.9226 | 0.93 | ( 0.20, 4.38) | 0.92 | ( 0.18, 4.79) | 0.00 | (-0.09, 0.09) | |
| Asia | 234 | 6 | 2.6 | 251 | 11 | 4.4 | 0.2766 | 1.71 | ( 0.64, 4.55) | 1.74 | ( 0.63, 4.79) | 0.02 | (-0.01, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6447 |
| <30 | 554 | 26 | 4.7 | 566 | 31 | 5.5 | 0.5506 | 1.17 | ( 0.70, 1.94) | 1.18 | ( 0.69, 2.01) | 0.01 | (-0.02, 0.03) | |
| >=30 | 634 | 47 | 7.4 | 605 | 45 | 7.4 | 0.9867 | 1.00 | ( 0.68, 1.49) | 1.00 | ( 0.66, 1.53) | 0.00 | (-0.03, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3143 |
| <130 | 379 | 33 | 8.7 | 382 | 29 | 7.6 | 0.5738 | 0.87 | ( 0.54, 1.41) | 0.86 | ( 0.51, 1.45) | -0.01 | (-0.05, 0.03) | |
| >=130 | 809 | 40 | 4.9 | 789 | 47 | 6.0 | 0.3724 | 1.20 | ( 0.80, 1.82) | 1.22 | ( 0.79, 1.88) | 0.01 | (-0.01, 0.03) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6453 |
| <75 | 500 | 37 | 7.4 | 500 | 34 | 6.8 | 0.7118 | 0.92 | ( 0.59, 1.44) | 0.91 | ( 0.56, 1.48) | -0.01 | (-0.04, 0.03) | |
| 75 to <85 | 427 | 25 | 5.9 | 417 | 31 | 7.4 | 0.3567 | 1.27 | ( 0.76, 2.11) | 1.29 | ( 0.75, 2.23) | 0.02 | (-0.02, 0.05) | |
| >=85 | 261 | 11 | 4.2 | 254 | 11 | 4.3 | 0.9480 | 1.03 | ( 0.45, 2.33) | 1.03 | ( 0.44, 2.42) | 0.00 | (-0.03, 0.04) | |
| History of heart failure | | | | | | | | | | | | | | 0.6996 |
| No | 1048 | 58 | 5.5 | 1031 | 62 | 6.0 | 0.6395 | 1.09 | ( 0.77, 1.54) | 1.09 | ( 0.76, 1.58) | 0.00 | (-0.02, 0.02) | |
| Yes | 140 | 15 | 10.7 | 140 | 14 | 10.0 | 0.8445 | 0.93 | ( 0.47, 1.86) | 0.93 | ( 0.43, 2.00) | -0.01 | (-0.08, 0.06) | |

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| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2220 |
| <45 | 179 | 17 | 9.5 | 178 | 12 | 6.7 | 0.3406 | 0.71 | ( 0.35, 1.44) | 0.69 | ( 0.32, 1.49) | -0.03 | (-0.08, 0.03) | |
| >=45 | 1009 | 56 | 5.6 | 993 | 64 | 6.4 | 0.3989 | 1.16 | ( 0.82, 1.64) | 1.17 | ( 0.81, 1.70) | 0.01 | (-0.01, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7863 |
| Normal (<30) | 250 | 25 | 10.0 | 257 | 23 | 8.9 | 0.6862 | 0.89 | ( 0.52, 1.53) | 0.88 | ( 0.49, 1.60) | -0.01 | (-0.06, 0.04) | |
| Microalbuminuria (30 to <=300) | 675 | 35 | 5.2 | 645 | 33 | 5.1 | 0.9549 | 0.99 | ( 0.62, 1.57) | 0.99 | ( 0.61, 1.61) | 0.00 | (-0.02, 0.02) | |
| Macroalbuminuria (>300) | 260 | 13 | 5.0 | 261 | 16 | 6.1 | 0.5737 | 1.23 | ( 0.60, 2.50) | 1.24 | ( 0.58, 2.63) | 0.01 | (-0.03, 0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7644 |
| Low, moderate or high | 1018 | 61 | 6.0 | 1001 | 59 | 5.9 | 0.9258 | 0.98 | ( 0.70, 1.39) | 0.98 | ( 0.68, 1.42) | 0.00 | (-0.02, 0.02) | |
| Very high | 167 | 12 | 7.2 | 162 | 13 | 8.0 | 0.7740 | 1.12 | ( 0.53, 2.37) | 1.13 | ( 0.50, 2.55) | 0.01 | (-0.05, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.8325 |
| No | 205 | 10 | 4.9 | 211 | 10 | 4.7 | 0.9473 | 0.97 | ( 0.41, 2.28) | 0.97 | ( 0.40, 2.38) | 0.00 | (-0.04, 0.04) | |
| Yes | 983 | 63 | 6.4 | 960 | 66 | 6.9 | 0.6799 | 1.07 | ( 0.77, 1.50) | 1.08 | ( 0.75, 1.54) | 0.00 | (-0.02, 0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7412 |
| No | 422 | 17 | 4.0 | 408 | 19 | 4.7 | 0.6568 | 1.16 | ( 0.61, 2.19) | 1.16 | ( 0.60, 2.27) | 0.01 | (-0.02, 0.03) | |
| Yes | 766 | 56 | 7.3 | 763 | 57 | 7.5 | 0.9049 | 1.02 | ( 0.72, 1.46) | 1.02 | ( 0.70, 1.50) | 0.00 | (-0.02, 0.03) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3119 |
| No | 629 | 24 | 3.8 | 589 | 29 | 4.9 | 0.3435 | 1.29 | ( 0.76, 2.19) | 1.31 | ( 0.75, 2.27) | 0.01 | (-0.01, 0.03) | |
| Yes | 559 | 49 | 8.8 | 582 | 47 | 8.1 | 0.6747 | 0.92 | ( 0.63, 1.35) | 0.91 | ( 0.60, 1.39) | -0.01 | (-0.04, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 132 | 11.1 | 1171 | 99 | 8.5 | 0.0299 | 0.76 | ( 0.59, 0.97) | 0.74 | ( 0.56, 0.97) | -0.03 | (-0.05, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4771 |
| Male | 864 | 95 | 11.0 | 837 | 74 | 8.8 | 0.1376 | 0.80 | ( 0.60, 1.07) | 0.79 | ( 0.57, 1.08) | -0.02 | (-0.05, 0.01) | |
| Female | 324 | 37 | 11.4 | 334 | 25 | 7.5 | 0.0841 | 0.66 | ( 0.40, 1.06) | 0.63 | ( 0.37, 1.07) | -0.04 | (-0.08, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.5580 |
| <65 | 569 | 57 | 10.0 | 547 | 38 | 6.9 | 0.0661 | 0.69 | ( 0.47, 1.03) | 0.67 | ( 0.44, 1.03) | -0.03 | (-0.06, 0.00) | |
| >=65 | 619 | 75 | 12.1 | 624 | 61 | 9.8 | 0.1862 | 0.81 | ( 0.59, 1.11) | 0.79 | ( 0.55, 1.12) | -0.02 | (-0.06, 0.01) | |
| Region | | | | | | | | | | | | | | 0.7605 |
| Europe | 468 | 40 | 8.5 | 434 | 29 | 6.7 | 0.2924 | 0.78 | ( 0.49, 1.24) | 0.77 | ( 0.47, 1.26) | -0.02 | (-0.05, 0.02) | |
| North America | 259 | 36 | 13.9 | 241 | 22 | 9.1 | 0.0960 | 0.66 | ( 0.40, 1.08) | 0.62 | ( 0.35, 1.09) | -0.05 | (-0.10, 0.01) | |
| Latin America | 177 | 21 | 11.9 | 191 | 13 | 6.8 | 0.0941 | 0.57 | ( 0.30, 1.11) | 0.54 | ( 0.26, 1.12) | -0.05 | (-0.11, 0.01) | |
| Africa | 50 | 11 | 22.0 | 54 | 11 | 20.4 | 0.8389 | 0.93 | ( 0.44, 1.94) | 0.91 | ( 0.35, 2.33) | -0.02 | (-0.17, 0.14) | |
| Asia | 234 | 24 | 10.3 | 251 | 24 | 9.6 | 0.7980 | 0.93 | ( 0.54, 1.60) | 0.93 | ( 0.51, 1.68) | -0.01 | (-0.06, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6247 |
| <30 | 554 | 63 | 11.4 | 566 | 52 | 9.2 | 0.2285 | 0.81 | ( 0.57, 1.14) | 0.79 | ( 0.54, 1.16) | -0.02 | (-0.06, 0.01) | |
| >=30 | 634 | 69 | 10.9 | 605 | 47 | 7.8 | 0.0599 | 0.71 | ( 0.50, 1.02) | 0.69 | ( 0.47, 1.02) | -0.03 | (-0.06, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6531 |
| <130 | 379 | 37 | 9.8 | 382 | 31 | 8.1 | 0.4257 | 0.83 | ( 0.53, 1.31) | 0.82 | ( 0.50, 1.35) | -0.02 | (-0.06, 0.02) | |
| >=130 | 809 | 95 | 11.7 | 789 | 68 | 8.6 | 0.0391 | 0.73 | ( 0.55, 0.99) | 0.71 | ( 0.51, 0.98) | -0.03 | (-0.06, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6679 |
| <75 | 500 | 55 | 11.0 | 500 | 45 | 9.0 | 0.2918 | 0.82 | ( 0.56, 1.19) | 0.80 | ( 0.53, 1.21) | -0.02 | (-0.06, 0.02) | |
| 75 to <85 | 427 | 53 | 12.4 | 417 | 34 | 8.2 | 0.0419 | 0.66 | ( 0.44, 0.99) | 0.63 | ( 0.40, 0.99) | -0.04 | (-0.08, 0.00) | |
| >=85 | 261 | 24 | 9.2 | 254 | 20 | 7.9 | 0.5917 | 0.86 | ( 0.49, 1.51) | 0.84 | ( 0.45, 1.57) | -0.01 | (-0.06, 0.04) | |
| History of heart failure | | | | | | | | | | | | | | 0.4900 |
| No | 1048 | 110 | 10.5 | 1031 | 79 | 7.7 | 0.0246 | 0.73 | ( 0.55, 0.96) | 0.71 | ( 0.52, 0.96) | -0.03 | (-0.05, 0.00) | |
| Yes | 140 | 22 | 15.7 | 140 | 20 | 14.3 | 0.7378 | 0.91 | ( 0.52, 1.59) | 0.89 | ( 0.46, 1.72) | -0.01 | (-0.10, 0.07) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8236 |
| <45 | 179 | 36 | 20.1 | 178 | 26 | 14.6 | 0.1698 | 0.73 | ( 0.46, 1.15) | 0.68 | ( 0.39, 1.18) | -0.06 | (-0.13, 0.02) | |
| >=45 | 1009 | 96 | 9.5 | 993 | 73 | 7.4 | 0.0818 | 0.77 | ( 0.58, 1.03) | 0.75 | ( 0.55, 1.04) | -0.02 | (-0.05, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3431 |
| Normal (<30) | 250 | 34 | 13.6 | 257 | 26 | 10.1 | 0.2248 | 0.74 | ( 0.46, 1.20) | 0.72 | ( 0.42, 1.23) | -0.03 | (-0.09, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 52 | 7.7 | 645 | 45 | 7.0 | 0.6129 | 0.91 | ( 0.62, 1.33) | 0.90 | ( 0.59, 1.36) | -0.01 | (-0.04, 0.02) | |
| Macroalbuminuria (>300) | 260 | 46 | 17.7 | 261 | 27 | 10.3 | 0.0157 | 0.58 | ( 0.38, 0.91) | 0.54 | ( 0.32, 0.89) | -0.07 | (-0.13,-0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8820 |
| Low, moderate or high | 1018 | 95 | 9.3 | 1001 | 70 | 7.0 | 0.0551 | 0.75 | ( 0.56, 1.01) | 0.73 | ( 0.53, 1.01) | -0.02 | (-0.05, 0.00) | |
| Very high | 167 | 37 | 22.2 | 162 | 28 | 17.3 | 0.2672 | 0.78 | ( 0.50, 1.21) | 0.73 | ( 0.42, 1.27) | -0.05 | (-0.13, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.8456 |
| No | 205 | 18 | 8.8 | 211 | 15 | 7.1 | 0.5282 | 0.81 | ( 0.42, 1.56) | 0.80 | ( 0.39, 1.62) | -0.02 | (-0.07, 0.04) | |
| Yes | 983 | 114 | 11.6 | 960 | 84 | 8.8 | 0.0381 | 0.75 | ( 0.58, 0.99) | 0.73 | ( 0.54, 0.98) | -0.03 | (-0.06, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4052 |
| No | 422 | 41 | 9.7 | 408 | 35 | 8.6 | 0.5701 | 0.88 | ( 0.57, 1.36) | 0.87 | ( 0.54, 1.40) | -0.01 | (-0.05, 0.03) | |
| Yes | 766 | 91 | 11.9 | 763 | 64 | 8.4 | 0.0237 | 0.71 | ( 0.52, 0.96) | 0.68 | ( 0.48, 0.95) | -0.03 | (-0.07, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4144 |
| No | 629 | 46 | 7.3 | 589 | 37 | 6.3 | 0.4753 | 0.86 | ( 0.57, 1.30) | 0.85 | ( 0.54, 1.33) | -0.01 | (-0.04, 0.02) | |
| Yes | 559 | 86 | 15.4 | 582 | 62 | 10.7 | 0.0174 | 0.69 | ( 0.51, 0.94) | 0.66 | ( 0.46, 0.93) | -0.05 | (-0.09,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 38 | 3.2 | 1171 | 41 | 3.5 | 0.6829 | 1.09 | ( 0.71, 1.69) | 1.10 | ( 0.70, 1.72) | 0.00 | (-0.01, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.3956 |
| Male | 864 | 29 | 3.4 | 837 | 34 | 4.1 | 0.4410 | 1.21 | ( 0.74, 1.97) | 1.22 | ( 0.74, 2.02) | 0.01 | (-0.01, 0.03) | |
| Female | 324 | 9 | 2.8 | 334 | 7 | 2.1 | 0.5702 | 0.75 | ( 0.28, 2.00) | 0.75 | ( 0.28, 2.04) | -0.01 | (-0.03, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.6951 |
| <65 | 569 | 10 | 1.8 | 547 | 12 | 2.2 | 0.6002 | 1.25 | ( 0.54, 2.87) | 1.25 | ( 0.54, 2.93) | 0.00 | (-0.01, 0.02) | |
| >=65 | 619 | 28 | 4.5 | 624 | 29 | 4.6 | 0.9168 | 1.03 | ( 0.62, 1.71) | 1.03 | ( 0.60, 1.75) | 0.00 | (-0.02, 0.02) | |
| Region | | | | | | | | | | | | | | 0.8719 |
| Europe | 468 | 15 | 3.2 | 434 | 15 | 3.5 | 0.8336 | 1.08 | ( 0.53, 2.18) | 1.08 | ( 0.52, 2.24) | 0.00 | (-0.02, 0.03) | |
| North America | 259 | 14 | 5.4 | 241 | 12 | 5.0 | 0.8302 | 0.92 | ( 0.43, 1.95) | 0.92 | ( 0.42, 2.02) | 0.00 | (-0.04, 0.03) | |
| Latin America | 177 | 1 | 0.6 | 191 | 2 | 1.0 | 0.6073 | 1.85 | ( 0.17,20.26) | 1.86 | ( 0.17,20.72) | 0.00 | (-0.01, 0.02) | |
| Africa | 50 | 2 | 4.0 | 54 | 5 | 9.3 | 0.2848 | 2.31 | ( 0.47,11.40) | 2.45 | ( 0.45,13.24) | 0.05 | (-0.04, 0.15) | |
| Asia | 234 | 6 | 2.6 | 251 | 7 | 2.8 | 0.8783 | 1.09 | ( 0.37, 3.19) | 1.09 | ( 0.36, 3.29) | 0.00 | (-0.03, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1706 |
| <30 | 554 | 19 | 3.4 | 566 | 15 | 2.7 | 0.4472 | 0.77 | ( 0.40, 1.51) | 0.77 | ( 0.39, 1.52) | -0.01 | (-0.03, 0.01) | |
| >=30 | 634 | 19 | 3.0 | 605 | 26 | 4.3 | 0.2212 | 1.43 | ( 0.80, 2.56) | 1.45 | ( 0.80, 2.65) | 0.01 | (-0.01, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1967 |
| <130 | 379 | 13 | 3.4 | 382 | 9 | 2.4 | 0.3766 | 0.69 | ( 0.30, 1.59) | 0.68 | ( 0.29, 1.61) | -0.01 | (-0.03, 0.01) | |
| >=130 | 809 | 25 | 3.1 | 789 | 32 | 4.1 | 0.2981 | 1.31 | ( 0.79, 2.19) | 1.33 | ( 0.78, 2.26) | 0.01 | (-0.01, 0.03) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1091 |
| <75 | 500 | 15 | 3.0 | 500 | 23 | 4.6 | 0.1858 | 1.53 | ( 0.81, 2.90) | 1.56 | ( 0.80, 3.02) | 0.02 | (-0.01, 0.04) | |
| 75 to <85 | 427 | 18 | 4.2 | 417 | 10 | 2.4 | 0.1405 | 0.57 | ( 0.27, 1.22) | 0.56 | ( 0.25, 1.22) | -0.02 | (-0.04, 0.01) | |
| >=85 | 261 | 5 | 1.9 | 254 | 8 | 3.1 | 0.3721 | 1.64 | ( 0.55, 4.96) | 1.67 | ( 0.54, 5.16) | 0.01 | (-0.01, 0.04) | |
| History of heart failure | | | | | | | | | | | | | | 0.4192 |
| No | 1048 | 31 | 3.0 | 1031 | 36 | 3.5 | 0.4908 | 1.18 | ( 0.74, 1.89) | 1.19 | ( 0.73, 1.93) | 0.01 | (-0.01, 0.02) | |
| Yes | 140 | 7 | 5.0 | 140 | 5 | 3.6 | 0.5551 | 0.71 | ( 0.23, 2.20) | 0.70 | ( 0.22, 2.27) | -0.01 | (-0.06, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6454 |
| <45 | 179 | 12 | 6.7 | 178 | 15 | 8.4 | 0.5381 | 1.26 | ( 0.61, 2.61) | 1.28 | ( 0.58, 2.82) | 0.02 | (-0.04, 0.07) | |
| >=45 | 1009 | 26 | 2.6 | 993 | 26 | 2.6 | 0.9534 | 1.02 | ( 0.59, 1.74) | 1.02 | ( 0.59, 1.76) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8005 |
| Normal (<30) | 250 | 12 | 4.8 | 257 | 16 | 6.2 | 0.4823 | 1.30 | ( 0.63, 2.69) | 1.32 | ( 0.61, 2.84) | 0.01 | (-0.03, 0.05) | |
| Microalbuminuria (30 to <=300) | 675 | 17 | 2.5 | 645 | 15 | 2.3 | 0.8198 | 0.92 | ( 0.47, 1.83) | 0.92 | ( 0.46, 1.86) | 0.00 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 260 | 9 | 3.5 | 261 | 10 | 3.8 | 0.8218 | 1.11 | ( 0.46, 2.68) | 1.11 | ( 0.44, 2.78) | 0.00 | (-0.03, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7618 |
| Low, moderate or high | 1018 | 27 | 2.7 | 1001 | 28 | 2.8 | 0.8415 | 1.05 | ( 0.63, 1.78) | 1.06 | ( 0.62, 1.81) | 0.00 | (-0.01, 0.02) | |
| Very high | 167 | 11 | 6.6 | 162 | 13 | 8.0 | 0.6161 | 1.22 | ( 0.56, 2.64) | 1.24 | ( 0.54, 2.85) | 0.01 | (-0.04, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9454 |
| No | 205 | 6 | 2.9 | 211 | 7 | 3.3 | 0.8189 | 1.13 | ( 0.39, 3.32) | 1.14 | ( 0.38, 3.45) | 0.00 | (-0.03, 0.04) | |
| Yes | 983 | 32 | 3.3 | 960 | 34 | 3.5 | 0.7276 | 1.09 | ( 0.68, 1.75) | 1.09 | ( 0.67, 1.78) | 0.00 | (-0.01, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.0801 |
| No | 422 | 9 | 2.1 | 408 | 17 | 4.2 | 0.0926 | 1.95 | ( 0.88, 4.33) | 2.00 | ( 0.88, 4.53) | 0.02 | ( 0.00, 0.04) | |
| Yes | 766 | 29 | 3.8 | 763 | 24 | 3.1 | 0.4937 | 0.83 | ( 0.49, 1.41) | 0.83 | ( 0.48, 1.43) | -0.01 | (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3533 |
| No | 629 | 12 | 1.9 | 589 | 16 | 2.7 | 0.3467 | 1.42 | ( 0.68, 2.98) | 1.44 | ( 0.67, 3.06) | 0.01 | (-0.01, 0.03) | |
| Yes | 559 | 26 | 4.7 | 582 | 25 | 4.3 | 0.7713 | 0.92 | ( 0.54, 1.58) | 0.92 | ( 0.52, 1.61) | 0.00 | (-0.03, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 71 | 6.0 | 1171 | 33 | 2.8 | 0.0002 | 0.47 | ( 0.31, 0.71) | 0.46 | ( 0.30, 0.70) | -0.03 | (-0.05,-0.02) | |
| Sex | | | | | | | | | | | | | | 0.5731 |
| Male | 864 | 50 | 5.8 | 837 | 21 | 2.5 | 0.0007 | 0.43 | ( 0.26, 0.72) | 0.42 | ( 0.25, 0.70) | -0.03 | (-0.05,-0.01) | |
| Female | 324 | 21 | 6.5 | 334 | 12 | 3.6 | 0.0896 | 0.55 | ( 0.28, 1.11) | 0.54 | ( 0.26, 1.11) | -0.03 | (-0.06, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.1025 |
| <65 | 569 | 32 | 5.6 | 547 | 9 | 1.6 | 0.0004 | 0.29 | ( 0.14, 0.61) | 0.28 | ( 0.13, 0.59) | -0.04 | (-0.06,-0.02) | |
| >=65 | 619 | 39 | 6.3 | 624 | 24 | 3.8 | 0.0486 | 0.61 | ( 0.37,>1.00) | 0.59 | ( 0.35, 1.00) | -0.02 | (-0.05, 0.00) | |
| Region | | | | | | | | | | | | | | 0.8146 |
| Europe | 468 | 22 | 4.7 | 434 | 12 | 2.8 | 0.1272 | 0.59 | ( 0.29, 1.17) | 0.58 | ( 0.28, 1.18) | -0.02 | (-0.04, 0.01) | |
| North America | 259 | 17 | 6.6 | 241 | 9 | 3.7 | 0.1545 | 0.57 | ( 0.26, 1.25) | 0.55 | ( 0.24, 1.26) | -0.03 | (-0.07, 0.01) | |
| Latin America | 177 | 12 | 6.8 | 191 | 5 | 2.6 | 0.0574 | 0.39 | ( 0.14, 1.07) | 0.37 | ( 0.13, 1.07) | -0.04 | (-0.09, 0.00) | |
| Africa | 50 | 2 | 4.0 | 54 | 1 | 1.9 | 0.5131 | 0.46 | ( 0.04, 4.95) | 0.45 | ( 0.04, 5.15) | -0.02 | (-0.09, 0.04) | |
| Asia | 234 | 18 | 7.7 | 251 | 6 | 2.4 | 0.0071 | 0.31 | ( 0.13, 0.77) | 0.29 | ( 0.11, 0.75) | -0.05 | (-0.09,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6318 |
| <30 | 554 | 34 | 6.1 | 566 | 18 | 3.2 | 0.0187 | 0.52 | ( 0.30, 0.91) | 0.50 | ( 0.28, 0.90) | -0.03 | (-0.05, 0.00) | |
| >=30 | 634 | 37 | 5.8 | 605 | 15 | 2.5 | 0.0032 | 0.42 | ( 0.24, 0.77) | 0.41 | ( 0.22, 0.76) | -0.03 | (-0.06,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9881 |
| <130 | 379 | 19 | 5.0 | 382 | 9 | 2.4 | 0.0516 | 0.47 | ( 0.22, 1.03) | 0.46 | ( 0.20, 1.02) | -0.03 | (-0.05, 0.00) | |
| >=130 | 809 | 52 | 6.4 | 789 | 24 | 3.0 | 0.0015 | 0.47 | ( 0.29, 0.76) | 0.46 | ( 0.28, 0.75) | -0.03 | (-0.05,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6279 |
| <75 | 500 | 35 | 7.0 | 500 | 19 | 3.8 | 0.0252 | 0.54 | ( 0.31, 0.94) | 0.52 | ( 0.30, 0.93) | -0.03 | (-0.06, 0.00) | |
| 75 to <85 | 427 | 24 | 5.6 | 417 | 8 | 1.9 | 0.0049 | 0.34 | ( 0.16, 0.75) | 0.33 | ( 0.15, 0.74) | -0.04 | (-0.06,-0.01) | |
| >=85 | 261 | 12 | 4.6 | 254 | 6 | 2.4 | 0.1673 | 0.51 | ( 0.20, 1.35) | 0.50 | ( 0.19, 1.36) | -0.02 | (-0.05, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.4907 |
| No | 1048 | 58 | 5.5 | 1031 | 25 | 2.4 | 0.0003 | 0.44 | ( 0.28, 0.69) | 0.42 | ( 0.26, 0.68) | -0.03 | (-0.05,-0.01) | |
| Yes | 140 | 13 | 9.3 | 140 | 8 | 5.7 | 0.2566 | 0.62 | ( 0.26, 1.44) | 0.59 | ( 0.24, 1.48) | -0.04 | (-0.10, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7070 |
| <45 | 179 | 15 | 8.4 | 178 | 6 | 3.4 | 0.0443 | 0.40 | ( 0.16, 1.01) | 0.38 | ( 0.14, 1.01) | -0.05 | (-0.10, 0.00) | |
| >=45 | 1009 | 56 | 5.6 | 993 | 27 | 2.7 | 0.0015 | 0.49 | ( 0.31, 0.77) | 0.48 | ( 0.30, 0.76) | -0.03 | (-0.05,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5617 |
| Normal (<30) | 250 | 15 | 6.0 | 257 | 9 | 3.5 | 0.1854 | 0.58 | ( 0.26, 1.31) | 0.57 | ( 0.24, 1.32) | -0.02 | (-0.06, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 34 | 5.0 | 645 | 16 | 2.5 | 0.0150 | 0.49 | ( 0.27, 0.88) | 0.48 | ( 0.26, 0.88) | -0.03 | (-0.05,-0.01) | |
| Macroalbuminuria (>300) | 260 | 22 | 8.5 | 261 | 7 | 2.7 | 0.0040 | 0.32 | ( 0.14, 0.73) | 0.30 | ( 0.13, 0.71) | -0.06 | (-0.10,-0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9362 |
| Low, moderate or high | 1018 | 58 | 5.7 | 1001 | 26 | 2.6 | 0.0005 | 0.46 | ( 0.29, 0.72) | 0.44 | ( 0.28, 0.71) | -0.03 | (-0.05,-0.01) | |
| Very high | 167 | 13 | 7.8 | 162 | 6 | 3.7 | 0.1127 | 0.48 | ( 0.19, 1.22) | 0.46 | ( 0.17, 1.23) | -0.04 | (-0.09, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3558 |
| No | 205 | 18 | 8.8 | 211 | 6 | 2.8 | 0.0094 | 0.32 | ( 0.13, 0.80) | 0.30 | ( 0.12, 0.78) | -0.06 | (-0.10,-0.01) | |
| Yes | 983 | 53 | 5.4 | 960 | 27 | 2.8 | 0.0042 | 0.52 | ( 0.33, 0.82) | 0.51 | ( 0.32, 0.81) | -0.03 | (-0.04,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7693 |
| No | 422 | 20 | 4.7 | 408 | 10 | 2.5 | 0.0774 | 0.52 | ( 0.25, 1.09) | 0.51 | ( 0.23, 1.09) | -0.02 | (-0.05, 0.00) | |
| Yes | 766 | 51 | 6.7 | 763 | 23 | 3.0 | 0.0009 | 0.45 | ( 0.28, 0.73) | 0.44 | ( 0.26, 0.72) | -0.04 | (-0.06,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2484 |
| No | 629 | 30 | 4.8 | 589 | 17 | 2.9 | 0.0882 | 0.61 | ( 0.34, 1.09) | 0.59 | ( 0.32, 1.09) | -0.02 | (-0.04, 0.00) | |
| Yes | 559 | 41 | 7.3 | 582 | 16 | 2.7 | 0.0004 | 0.37 | ( 0.21, 0.66) | 0.36 | ( 0.20, 0.64) | -0.05 | (-0.07,-0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: $Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 29 | 2.4 | 1171 | 22 | 1.9 | 0.3478 | 0.77 | ( 0.44, 1.33) | 0.77 | ( 0.44, 1.34) | -0.01 | (-0.02, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.4875 |
| Male | 864 | 19 | 2.2 | 837 | 12 | 1.4 | 0.2381 | 0.65 | ( 0.32, 1.33) | 0.65 | ( 0.31, 1.34) | -0.01 | (-0.02, 0.01) | |
| Female | 324 | 10 | 3.1 | 334 | 10 | 3.0 | 0.9450 | 0.97 | ( 0.41, 2.30) | 0.97 | ( 0.40, 2.36) | 0.00 | (-0.03, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.9606 |
| <65 | 569 | 12 | 2.1 | 547 | 9 | 1.6 | 0.5688 | 0.78 | ( 0.33, 1.84) | 0.78 | ( 0.32, 1.86) | 0.00 | (-0.02, 0.01) | |
| >=65 | 619 | 17 | 2.7 | 624 | 13 | 2.1 | 0.4463 | 0.76 | ( 0.37, 1.55) | 0.75 | ( 0.36, 1.56) | -0.01 | (-0.02, 0.01) | |
| Region | | | | | | | | | | | | | | 0.7777 |
| Europe | 468 | 7 | 1.5 | 434 | 3 | 0.7 | 0.2489 | 0.46 | ( 0.12, 1.78) | 0.46 | ( 0.12, 1.78) | -0.01 | (-0.02, 0.01) | |
| North America | 259 | 10 | 3.9 | 241 | 6 | 2.5 | 0.3840 | 0.64 | ( 0.24, 1.75) | 0.64 | ( 0.23, 1.78) | -0.01 | (-0.04, 0.02) | |
| Latin America | 177 | 5 | 2.8 | 191 | 5 | 2.6 | 0.9029 | 0.93 | ( 0.27, 3.15) | 0.92 | ( 0.26, 3.25) | 0.00 | (-0.04, 0.03) | |
| Africa | 50 | 2 | 4.0 | 54 | 1 | 1.9 | 0.5131 | 0.46 | ( 0.04, 4.95) | 0.45 | ( 0.04, 5.15) | -0.02 | (-0.09, 0.04) | |
| Asia | 234 | 5 | 2.1 | 251 | 7 | 2.8 | 0.6441 | 1.31 | ( 0.42, 4.06) | 1.31 | ( 0.41, 4.20) | 0.01 | (-0.02, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9985 |
| <30 | 554 | 18 | 3.2 | 566 | 14 | 2.5 | 0.4360 | 0.76 | ( 0.38, 1.52) | 0.76 | ( 0.37, 1.53) | -0.01 | (-0.03, 0.01) | |
| >=30 | 634 | 11 | 1.7 | 605 | 8 | 1.3 | 0.5546 | 0.76 | ( 0.31, 1.88) | 0.76 | ( 0.30, 1.90) | 0.00 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3681 |
| <130 | 379 | 7 | 1.8 | 382 | 8 | 2.1 | 0.8062 | 1.13 | ( 0.42, 3.10) | 1.14 | ( 0.41, 3.17) | 0.00 | (-0.02, 0.02) | |
| >=130 | 809 | 22 | 2.7 | 789 | 14 | 1.8 | 0.2031 | 0.65 | ( 0.34, 1.27) | 0.65 | ( 0.33, 1.27) | -0.01 | (-0.02, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6778 |
| <75 | 500 | 17 | 3.4 | 500 | 13 | 2.6 | 0.4584 | 0.76 | ( 0.38, 1.56) | 0.76 | ( 0.36, 1.58) | -0.01 | (-0.03, 0.01) | |
| 75 to <85 | 427 | 10 | 2.3 | 417 | 6 | 1.4 | 0.3361 | 0.61 | ( 0.23, 1.68) | 0.61 | ( 0.22, 1.69) | -0.01 | (-0.03, 0.01) | |
| >=85 | 261 | 2 | 0.8 | 254 | 3 | 1.2 | 0.6312 | 1.54 | ( 0.26, 9.15) | 1.55 | ( 0.26, 9.34) | 0.00 | (-0.01, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.4186 |
| No | 1048 | 28 | 2.7 | 1031 | 20 | 1.9 | 0.2666 | 0.73 | ( 0.41, 1.28) | 0.72 | ( 0.40, 1.29) | -0.01 | (-0.02, 0.01) | |
| Yes | 140 | 1 | 0.7 | 140 | 2 | 1.4 | 0.5616 | 2.00 | ( 0.18,21.81) | 2.01 | ( 0.18,22.47) | 0.01 | (-0.02, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: $Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4659 |
| <45 | 179 | 12 | 6.7 | 178 | 7 | 3.9 | 0.2435 | 0.59 | ( 0.24, 1.46) | 0.57 | ( 0.22, 1.48) | -0.03 | (-0.07, 0.02) | |
| >=45 | 1009 | 17 | 1.7 | 993 | 15 | 1.5 | 0.7559 | 0.90 | ( 0.45, 1.79) | 0.89 | ( 0.44, 1.80) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4487 |
| Normal (<30) | 250 | 8 | 3.2 | 257 | 4 | 1.6 | 0.2236 | 0.49 | ( 0.15, 1.59) | 0.48 | ( 0.14, 1.61) | -0.02 | (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 10 | 1.5 | 645 | 11 | 1.7 | 0.7451 | 1.15 | ( 0.49, 2.69) | 1.15 | ( 0.49, 2.74) | 0.00 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 260 | 11 | 4.2 | 261 | 7 | 2.7 | 0.3331 | 0.63 | ( 0.25, 1.61) | 0.62 | ( 0.24, 1.64) | -0.02 | (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4908 |
| Low, moderate or high | 1018 | 17 | 1.7 | 1001 | 15 | 1.5 | 0.7578 | 0.90 | ( 0.45, 1.79) | 0.90 | ( 0.44, 1.80) | 0.00 | (-0.01, 0.01) | |
| Very high | 167 | 12 | 7.2 | 162 | 7 | 4.3 | 0.2655 | 0.60 | ( 0.24, 1.49) | 0.58 | ( 0.22, 1.52) | -0.03 | (-0.08, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4606 |
| No | 205 | 2 | 1.0 | 211 | 3 | 1.4 | 0.6763 | 1.46 | ( 0.25, 8.63) | 1.46 | ( 0.24, 8.85) | 0.00 | (-0.02, 0.03) | |
| Yes | 983 | 27 | 2.7 | 960 | 19 | 2.0 | 0.2659 | 0.72 | ( 0.40, 1.29) | 0.71 | ( 0.39, 1.29) | -0.01 | (-0.02, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8793 |
| No | 422 | 10 | 2.4 | 408 | 7 | 1.7 | 0.5061 | 0.72 | ( 0.28, 1.88) | 0.72 | ( 0.27, 1.91) | -0.01 | (-0.03, 0.01) | |
| Yes | 766 | 19 | 2.5 | 763 | 15 | 2.0 | 0.4951 | 0.79 | ( 0.41, 1.55) | 0.79 | ( 0.40, 1.56) | -0.01 | (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8790 |
| No | 629 | 12 | 1.9 | 589 | 9 | 1.5 | 0.6109 | 0.80 | ( 0.34, 1.89) | 0.80 | ( 0.33, 1.91) | 0.00 | (-0.02, 0.01) | |
| Yes | 559 | 17 | 3.0 | 582 | 13 | 2.2 | 0.3941 | 0.73 | ( 0.36, 1.50) | 0.73 | ( 0.35, 1.51) | -0.01 | (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Lower Limb Amputations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 0 | 0 | 1171 | 0 | 0 | | | | | |
| Sex | | | | | | | | | | | |
| Male | 864 | 0 | 0 | 837 | 0 | 0 | | | | | |
| Female | 324 | 0 | 0 | 334 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 0 | 0 | 547 | 0 | 0 | | | | | |
| >=65 | 619 | 0 | 0 | 624 | 0 | 0 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 0 | 0 | 434 | 0 | 0 | | | | | |
| North America | 259 | 0 | 0 | 241 | 0 | 0 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 0 | 0 | 566 | 0 | 0 | | | | | |
| >=30 | 634 | 0 | 0 | 605 | 0 | 0 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 382 | 0 | 0 | | | | | |
| >=130 | 809 | 0 | 0 | 789 | 0 | 0 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 0 | 0 | 500 | 0 | 0 | | | | | |
| 75 to <85 | 427 | 0 | 0 | 417 | 0 | 0 | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 0 | 0 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 0 | 0 | 1031 | 0 | 0 | | | | | |
| Yes | 140 | 0 | 0 | 140 | 0 | 0 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Lower Limb Amputations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 178 | 0 | 0 | | | | | |
| >=45 | 1009 | 0 | 0 | 993 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 0 | 0 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 0 | 0 | 645 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 0 | 0 | 1001 | 0 | 0 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 0 | 0 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 0 | 0 | 960 | 0 | 0 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 0 | 0 | 408 | 0 | 0 | | | | | |
| Yes | 766 | 0 | 0 | 763 | 0 | 0 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 0 | 0 | 589 | 0 | 0 | | | | | |
| Yes | 559 | 0 | 0 | 582 | 0 | 0 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 4 | 0.3 | 1171 | 5 | 0.4 | 0.7221 | 1.27 ( 0.34, 4.71) | 1.27 ( 0.34, 4.74) | 0.00 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | |
| Male | 864 | 1 | 0.1 | 837 | 3 | 0.4 | | | | | |
| Female | 324 | 3 | 0.9 | 334 | 2 | 0.6 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 2 | 0.4 | 547 | 2 | 0.4 | | | | | |
| >=65 | 619 | 2 | 0.3 | 624 | 3 | 0.5 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 2 | 0.4 | 434 | 2 | 0.5 | | | | | |
| North America | 259 | 0 | 0 | 241 | 1 | 0.4 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 2 | 1.0 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | |
| Asia | 234 | 2 | 0.9 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 3 | 0.5 | 566 | 2 | 0.4 | | | | | |
| >=30 | 634 | 1 | 0.2 | 605 | 3 | 0.5 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 2 | 0.5 | 382 | 1 | 0.3 | | | | | |
| >=130 | 809 | 2 | 0.2 | 789 | 4 | 0.5 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 2 | 0.4 | 500 | 1 | 0.2 | | | | | |
| 75 to <85 | 427 | 2 | 0.5 | 417 | 3 | 0.7 | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 1 | 0.4 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 3 | 0.3 | 1031 | 4 | 0.4 | | | | | |
| Yes | 140 | 1 | 0.7 | 140 | 1 | 0.7 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 1 | 0.6 | 178 | 1 | 0.6 | | | | | |
| >=45 | 1009 | 3 | 0.3 | 993 | 4 | 0.4 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 1 | 0.4 | 257 | 1 | 0.4 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 2 | 0.3 | 645 | 3 | 0.5 | | | | | |
| Macroalbuminuria (>300) | 260 | 1 | 0.4 | 261 | 1 | 0.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 4 | 0.4 | 1001 | 5 | 0.5 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 2 | 1.0 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 2 | 0.2 | 960 | 5 | 0.5 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 1 | 0.2 | 408 | 2 | 0.5 | | | | | |
| Yes | 766 | 3 | 0.4 | 763 | 3 | 0.4 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 1 | 0.2 | 589 | 4 | 0.7 | | | | | |
| Yes | 559 | 3 | 0.5 | 582 | 1 | 0.2 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Ketoacidosis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 0 | 0 | 1171 | 3 | 0.3 | 0.1296 | 7.10 ( 0.37,137.33) | 7.12 ( 0.37,137.99) | 0.00 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | |
| Male | 864 | 0 | 0 | 837 | 3 | 0.4 | | | | | |
| Female | 324 | 0 | 0 | 334 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 0 | 0 | 547 | 1 | 0.2 | | | | | |
| >=65 | 619 | 0 | 0 | 624 | 2 | 0.3 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 0 | 0 | 434 | 1 | 0.2 | | | | | |
| North America | 259 | 0 | 0 | 241 | 1 | 0.4 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 1 | 1.9 | | | | | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 0 | 0 | 566 | 2 | 0.4 | | | | | |
| >=30 | 634 | 0 | 0 | 605 | 1 | 0.2 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 382 | 0 | 0 | | | | | |
| >=130 | 809 | 0 | 0 | 789 | 3 | 0.4 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 0 | 0 | 500 | 1 | 0.2 | | | | | |
| 75 to <85 | 427 | 0 | 0 | 417 | 0 | 0 | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 2 | 0.8 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 0 | 0 | 1031 | 3 | 0.3 | | | | | |
| Yes | 140 | 0 | 0 | 140 | 0 | 0 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 178 | 0 | 0 | | | | | |
| >=45 | 1009 | 0 | 0 | 993 | 3 | 0.3 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 0 | 0 | 257 | 1 | 0.4 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 0 | 0 | 645 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 1 | 0.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 0 | 0 | 1001 | 3 | 0.3 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 0 | 0 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 0 | 0 | 960 | 3 | 0.3 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 0 | 0 | 408 | 1 | 0.2 | | | | | |
| Yes | 766 | 0 | 0 | 763 | 2 | 0.3 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 0 | 0 | 589 | 0 | 0 | | | | | |
| Yes | 559 | 0 | 0 | 582 | 3 | 0.5 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 16 | 1.3 | 1171 | 6 | 0.5 | 0.0350 | 0.38 | ( 0.15, | 0.97) | 0.38 | ( 0.15, | 0.97) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.1624 |
| Male | 864 | 11 | 1.3 | 837 | 2 | 0.2 | 0.0143 | 0.19 | ( 0.04, | 0.84) | 0.19 | ( 0.04, | 0.84) | -0.01 | (-0.02, 0.00) | |
| Female | 324 | 5 | 1.5 | 334 | 4 | 1.2 | 0.7028 | 0.78 | ( 0.21, | 2.86) | 0.77 | ( 0.21, | 2.91) | 0.00 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | | | | 0.8933 |
| <65 | 569 | 6 | 1.1 | 547 | 2 | 0.4 | 0.1727 | 0.35 | ( 0.07, | 1.71) | 0.34 | ( 0.07, | 1.71) | -0.01 | (-0.02, 0.00) | |
| >=65 | 619 | 10 | 1.6 | 624 | 4 | 0.6 | 0.1036 | 0.40 | ( 0.13, | 1.26) | 0.39 | ( 0.12, | 1.26) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | | | |
| Europe | 468 | 6 | 1.3 | 434 | 0 | 0 | | | | | | | | | | |
| North America | 259 | 4 | 1.5 | 241 | 2 | 0.8 | | | | | | | | | | |
| Latin America | 177 | 1 | 0.6 | 191 | 2 | 1.0 | | | | | | | | | | |
| Africa | 50 | 2 | 4.0 | 54 | 0 | 0 | | | | | | | | | | |
| Asia | 234 | 3 | 1.3 | 251 | 2 | 0.8 | | | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.5306 |
| <30 | 554 | 8 | 1.4 | 566 | 4 | 0.7 | 0.2308 | 0.49 | ( 0.15, | 1.62) | 0.49 | ( 0.15, | 1.62) | -0.01 | (-0.02, 0.00) | |
| >=30 | 634 | 8 | 1.3 | 605 | 2 | 0.3 | 0.0671 | 0.26 | ( 0.06, | 1.23) | 0.26 | ( 0.05, | 1.23) | -0.01 | (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.8894 |
| <130 | 379 | 3 | 0.8 | 382 | 1 | 0.3 | 0.3122 | 0.33 | ( 0.03, | 3.17) | 0.33 | ( 0.03, | 3.18) | -0.01 | (-0.02, 0.00) | |
| >=130 | 809 | 13 | 1.6 | 789 | 5 | 0.6 | 0.0653 | 0.39 | ( 0.14, | 1.10) | 0.39 | ( 0.14, | 1.10) | -0.01 | (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.8752 |
| <75 | 500 | 10 | 2.0 | 500 | 4 | 0.8 | 0.1063 | 0.40 | ( 0.13, | 1.27) | 0.40 | ( 0.12, | 1.27) | -0.01 | (-0.03, 0.00) | |
| 75 to <85 | 427 | 4 | 0.9 | 417 | 2 | 0.5 | 0.4293 | 0.51 | ( 0.09, | 2.78) | 0.51 | ( 0.09, | 2.80) | 0.00 | (-0.02, 0.01) | |
| >=85 | 261 | 2 | 0.8 | 254 | 0 | 0 | 0.2565 | 0.21 | (<0.01, | 4.26) | 0.20 | (<0.01, | 4.27) | -0.01 | (-0.02, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | | | 0.6307 |
| No | 1048 | 14 | 1.3 | 1031 | 6 | 0.6 | 0.0783 | 0.44 | ( 0.17, | 1.13) | 0.43 | ( 0.17, | 1.13) | -0.01 | (-0.02, 0.00) | |
| Yes | 140 | 2 | 1.4 | 140 | 0 | 0 | 0.2457 | 0.20 | (<0.01, | 4.13) | 0.20 | (<0.01, | 4.14) | -0.01 | (-0.04, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9913 |
| <45 | 179 | 8 | 4.5 | 178 | 3 | 1.7 | 0.1280 | 0.38 | ( 0.10, 1.40) | 0.37 | ( 0.10, 1.40) | -0.03 | (-0.06, 0.01) | |
| >=45 | 1009 | 8 | 0.8 | 993 | 3 | 0.3 | 0.1375 | 0.38 | ( 0.10, 1.43) | 0.38 | ( 0.10, 1.43) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4360 |
| Normal (<30) | 250 | 5 | 2.0 | 257 | 0 | 0 | 0.0368 | 0.09 | (<0.01, 1.59) | 0.09 | (<0.01, 1.58) | -0.02 | (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 7 | 1.0 | 645 | 3 | 0.5 | 0.2310 | 0.45 | ( 0.12, 1.73) | 0.45 | ( 0.11, 1.73) | -0.01 | (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 260 | 4 | 1.5 | 261 | 3 | 1.1 | 0.6998 | 0.75 | ( 0.17, 3.31) | 0.74 | ( 0.16, 3.36) | 0.00 | (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1401 |
| Low, moderate or high | 1018 | 11 | 1.1 | 1001 | 2 | 0.2 | 0.0134 | 0.18 | ( 0.04, 0.83) | 0.18 | ( 0.04, 0.83) | -0.01 | (-0.02, 0.00) | |
| Very high | 167 | 5 | 3.0 | 162 | 4 | 2.5 | 0.7704 | 0.82 | ( 0.23, 3.02) | 0.82 | ( 0.22, 3.11) | -0.01 | (-0.04, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6512 |
| No | 205 | 0 | 0 | 211 | 0 | 0 | 0.9885 | 0.97 | ( 0.02, 48.74) | 0.97 | ( 0.02, 49.20) | 0.00 | (-0.01, 0.01) | |
| Yes | 983 | 16 | 1.6 | 960 | 6 | 0.6 | 0.0368 | 0.38 | ( 0.15, 0.98) | 0.38 | ( 0.15, 0.98) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6970 |
| No | 422 | 4 | 0.9 | 408 | 1 | 0.2 | 0.1909 | 0.26 | ( 0.03, 2.30) | 0.26 | ( 0.03, 2.31) | -0.01 | (-0.02, 0.00) | |
| Yes | 766 | 12 | 1.6 | 763 | 5 | 0.7 | 0.0893 | 0.42 | ( 0.15, 1.18) | 0.41 | ( 0.15, 1.18) | -0.01 | (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5216 |
| No | 629 | 6 | 1.0 | 589 | 3 | 0.5 | 0.3653 | 0.53 | ( 0.13, 2.13) | 0.53 | ( 0.13, 2.14) | 0.00 | (-0.01, 0.01) | |
| Yes | 559 | 10 | 1.8 | 582 | 3 | 0.5 | 0.0428 | 0.29 | ( 0.08, 1.04) | 0.28 | ( 0.08, 1.04) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 21 | 1.8 | 1171 | 21 | 1.8 | 0.9624 | 1.01 | ( 0.56, 1.85) | 1.01 | ( 0.55, 1.87) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.6013 |
| Male | 864 | 11 | 1.3 | 837 | 9 | 1.1 | 0.7051 | 0.84 | ( 0.35, 2.03) | 0.84 | ( 0.35, 2.04) | 0.00 | (-0.01, 0.01) | |
| Female | 324 | 10 | 3.1 | 334 | 12 | 3.6 | 0.7179 | 1.16 | ( 0.51, 2.66) | 1.17 | ( 0.50, 2.75) | 0.01 | (-0.02, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.4503 |
| <65 | 569 | 5 | 0.9 | 547 | 7 | 1.3 | 0.5162 | 1.46 | ( 0.47, 4.56) | 1.46 | ( 0.46, 4.64) | 0.00 | (-0.01, 0.02) | |
| >=65 | 619 | 16 | 2.6 | 624 | 14 | 2.2 | 0.6951 | 0.87 | ( 0.43, 1.76) | 0.86 | ( 0.42, 1.79) | 0.00 | (-0.02, 0.01) | |
| Region | | | | | | | | | | | | | | 0.2927 |
| Europe | 468 | 10 | 2.1 | 434 | 3 | 0.7 | 0.0688 | 0.32 | ( 0.09, 1.17) | 0.32 | ( 0.09, 1.17) | -0.01 | (-0.03, 0.00) | |
| North America | 259 | 3 | 1.2 | 241 | 4 | 1.7 | 0.6335 | 1.43 | ( 0.32, 6.34) | 1.44 | ( 0.32, 6.50) | 0.01 | (-0.02, 0.03) | |
| Latin America | 177 | 2 | 1.1 | 191 | 6 | 3.1 | 0.1862 | 2.78 | ( 0.57, 13.59) | 2.84 | ( 0.57, 14.25) | 0.02 | (-0.01, 0.05) | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | 0.9697 | 0.93 | ( 0.02, 45.87) | 0.93 | ( 0.02, 47.58) | 0.00 | (-0.04, 0.04) | |
| Asia | 234 | 6 | 2.6 | 251 | 8 | 3.2 | 0.6821 | 1.24 | ( 0.44, 3.53) | 1.25 | ( 0.43, 3.66) | 0.01 | (-0.02, 0.04) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5948 |
| <30 | 554 | 12 | 2.2 | 566 | 14 | 2.5 | 0.7326 | 1.14 | ( 0.53, 2.45) | 1.15 | ( 0.53, 2.50) | 0.00 | (-0.01, 0.02) | |
| >=30 | 634 | 9 | 1.4 | 605 | 7 | 1.2 | 0.6824 | 0.82 | ( 0.31, 2.17) | 0.81 | ( 0.30, 2.20) | 0.00 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4096 |
| <130 | 379 | 5 | 1.3 | 382 | 3 | 0.8 | 0.4703 | 0.60 | ( 0.14, 2.47) | 0.59 | ( 0.14, 2.50) | -0.01 | (-0.02, 0.01) | |
| >=130 | 809 | 16 | 2.0 | 789 | 18 | 2.3 | 0.6741 | 1.15 | ( 0.59, 2.25) | 1.16 | ( 0.59, 2.29) | 0.00 | (-0.01, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7401 |
| <75 | 500 | 7 | 1.4 | 500 | 9 | 1.8 | 0.6142 | 1.29 | ( 0.48, 3.43) | 1.29 | ( 0.48, 3.49) | 0.00 | (-0.01, 0.02) | |
| 75 to <85 | 427 | 8 | 1.9 | 417 | 8 | 1.9 | 0.9618 | 1.02 | ( 0.39, 2.70) | 1.02 | ( 0.38, 2.76) | 0.00 | (-0.02, 0.02) | |
| >=85 | 261 | 6 | 2.3 | 254 | 4 | 1.6 | 0.5516 | 0.69 | ( 0.20, 2.40) | 0.68 | ( 0.19, 2.44) | -0.01 | (-0.03, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.1768 |
| No | 1048 | 17 | 1.6 | 1031 | 20 | 1.9 | 0.5838 | 1.20 | ( 0.63, 2.27) | 1.20 | ( 0.62, 2.30) | 0.00 | (-0.01, 0.01) | |
| Yes | 140 | 4 | 2.9 | 140 | 1 | 0.7 | 0.1758 | 0.25 | ( 0.03, 2.21) | 0.24 | ( 0.03, 2.22) | -0.02 | (-0.05, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4238 |
| <45 | 179 | 5 | 2.8 | 178 | 3 | 1.7 | 0.4795 | 0.60 | ( 0.15, 2.49) | 0.60 | ( 0.14, 2.53) | -0.01 | (-0.04, 0.02) | |
| >=45 | 1009 | 16 | 1.6 | 993 | 18 | 1.8 | 0.6943 | 1.14 | ( 0.59, 2.23) | 1.15 | ( 0.58, 2.26) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1233 |
| Normal (<30) | 250 | 6 | 2.4 | 257 | 1 | 0.4 | 0.0524 | 0.16 | ( 0.02, 1.34) | 0.16 | ( 0.02, 1.33) | -0.02 | (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 13 | 1.9 | 645 | 15 | 2.3 | 0.6145 | 1.21 | ( 0.58, 2.52) | 1.21 | ( 0.57, 2.57) | 0.00 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 260 | 2 | 0.8 | 261 | 5 | 1.9 | 0.2558 | 2.49 | ( 0.49, 12.72) | 2.52 | ( 0.48, 13.10) | 0.01 | (-0.01, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9861 |
| Low, moderate or high | 1018 | 17 | 1.7 | 1001 | 17 | 1.7 | 0.9605 | 1.02 | ( 0.52, 1.98) | 1.02 | ( 0.52, 2.00) | 0.00 | (-0.01, 0.01) | |
| Very high | 167 | 4 | 2.4 | 162 | 4 | 2.5 | 0.9653 | 1.03 | ( 0.26, 4.05) | 1.03 | ( 0.25, 4.20) | 0.00 | (-0.03, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9416 |
| No | 205 | 5 | 2.4 | 211 | 5 | 2.4 | 0.9632 | 0.97 | ( 0.29, 3.31) | 0.97 | ( 0.28, 3.40) | 0.00 | (-0.03, 0.03) | |
| Yes | 983 | 16 | 1.6 | 960 | 16 | 1.7 | 0.9462 | 1.02 | ( 0.52, 2.04) | 1.02 | ( 0.51, 2.06) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9615 |
| No | 422 | 9 | 2.1 | 408 | 9 | 2.2 | 0.9423 | 1.03 | ( 0.41, 2.58) | 1.04 | ( 0.41, 2.63) | 0.00 | (-0.02, 0.02) | |
| Yes | 766 | 12 | 1.6 | 763 | 12 | 1.6 | 0.9923 | 1.00 | ( 0.45, 2.22) | 1.00 | ( 0.45, 2.25) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1589 |
| No | 629 | 8 | 1.3 | 589 | 12 | 2.0 | 0.2935 | 1.60 | ( 0.66, 3.89) | 1.61 | ( 0.66, 3.98) | 0.01 | (-0.01, 0.02) | |
| Yes | 559 | 13 | 2.3 | 582 | 9 | 1.5 | 0.3387 | 0.66 | ( 0.29, 1.54) | 0.66 | ( 0.28, 1.56) | -0.01 | (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pylenophritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 11 | 0.9 | 1171 | 8 | 0.7 | 0.5096 | 0.74 | ( 0.30, 1.83) | 0.74 | ( 0.29, 1.84) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.2926 |
| Male | 864 | 7 | 0.8 | 837 | 3 | 0.4 | 0.2231 | 0.44 | ( 0.11, 1.71) | 0.44 | ( 0.11, 1.71) | 0.00 | (-0.01, 0.00) | |
| Female | 324 | 4 | 1.2 | 334 | 5 | 1.5 | 0.7720 | 1.21 | ( 0.33, 4.48) | 1.22 | ( 0.32, 4.57) | 0.00 | (-0.02, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.6879 |
| <65 | 569 | 2 | 0.4 | 547 | 2 | 0.4 | 0.9685 | 1.04 | ( 0.15, 7.36) | 1.04 | ( 0.15, 7.41) | 0.00 | (-0.01, 0.01) | |
| >=65 | 619 | 9 | 1.5 | 624 | 6 | 1.0 | 0.4266 | 0.66 | ( 0.24, 1.85) | 0.66 | ( 0.23, 1.86) | 0.00 | (-0.02, 0.01) | |
| Region | | | | | | | | | | | | | | |
| Europe | 468 | 4 | 0.9 | 434 | 1 | 0.2 | | | | | | | | |
| North America | 259 | 2 | 0.8 | 241 | 2 | 0.8 | | | | | | | | |
| Latin America | 177 | 1 | 0.6 | 191 | 1 | 0.5 | | | | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | | | | |
| Asia | 234 | 4 | 1.7 | 251 | 4 | 1.6 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9028 |
| <30 | 554 | 7 | 1.3 | 566 | 5 | 0.9 | 0.5367 | 0.70 | ( 0.22, 2.19) | 0.70 | ( 0.22, 2.21) | 0.00 | (-0.02, 0.01) | |
| >=30 | 634 | 4 | 0.6 | 605 | 3 | 0.5 | 0.7512 | 0.79 | ( 0.18, 3.50) | 0.78 | ( 0.17, 3.52) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8866 |
| <130 | 379 | 3 | 0.8 | 382 | 2 | 0.5 | 0.6473 | 0.66 | ( 0.11, 3.94) | 0.66 | ( 0.11, 3.97) | 0.00 | (-0.01, 0.01) | |
| >=130 | 809 | 8 | 1.0 | 789 | 6 | 0.8 | 0.6242 | 0.77 | ( 0.27, 2.21) | 0.77 | ( 0.26, 2.22) | 0.00 | (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | |
| <75 | 500 | 3 | 0.6 | 500 | 5 | 1.0 | | | | | | | | |
| 75 to <85 | 427 | 5 | 1.2 | 417 | 2 | 0.5 | | | | | | | | |
| >=85 | 261 | 3 | 1.1 | 254 | 1 | 0.4 | | | | | | | | |
| History of heart failure | | | | | | | | | | | | | | 0.3515 |
| No | 1048 | 9 | 0.9 | 1031 | 8 | 0.8 | 0.8339 | 0.90 | ( 0.35, 2.33) | 0.90 | ( 0.35, 2.35) | 0.00 | (-0.01, 0.01) | |
| Yes | 140 | 2 | 1.4 | 140 | 0 | 0 | 0.2457 | 0.20 | (<0.01, 4.13) | 0.20 | (<0.01, 4.14) | -0.01 | (-0.04, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pylenophritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9033 |
| <45 | 179 | 3 | 1.7 | 178 | 2 | 1.1 | 0.6570 | 0.67 | ( 0.11, 3.96) | 0.67 | ( 0.11, 4.04) | -0.01 | (-0.03, 0.02) | |
| >=45 | 1009 | 8 | 0.8 | 993 | 6 | 0.6 | 0.6126 | 0.76 | ( 0.27, 2.19) | 0.76 | ( 0.26, 2.20) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2109 |
| Normal (<30) | 250 | 4 | 1.6 | 257 | 0 | 0 | 0.0674 | 0.11 | (<0.01, 2.00) | 0.11 | (<0.01, 1.99) | -0.02 | (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 6 | 0.9 | 645 | 5 | 0.8 | 0.8203 | 0.87 | ( 0.27, 2.84) | 0.87 | ( 0.26, 2.87) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 260 | 1 | 0.4 | 261 | 3 | 1.1 | 0.3173 | 2.99 | ( 0.31, 28.54) | 3.01 | ( 0.31, 29.14) | 0.01 | (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3436 |
| Low, moderate or high | 1018 | 9 | 0.9 | 1001 | 5 | 0.5 | 0.2978 | 0.56 | ( 0.19, 1.68) | 0.56 | ( 0.19, 1.69) | 0.00 | (-0.01, 0.00) | |
| Very high | 167 | 2 | 1.2 | 162 | 3 | 1.9 | 0.6277 | 1.55 | ( 0.26, 9.13) | 1.56 | ( 0.26, 9.44) | 0.01 | (-0.02, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7080 |
| No | 205 | 2 | 1.0 | 211 | 1 | 0.5 | 0.5455 | 0.49 | ( 0.04, 5.32) | 0.48 | ( 0.04, 5.37) | -0.01 | (-0.02, 0.01) | |
| Yes | 983 | 9 | 0.9 | 960 | 7 | 0.7 | 0.6494 | 0.80 | ( 0.30, 2.13) | 0.79 | ( 0.29, 2.14) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2510 |
| No | 422 | 4 | 0.9 | 408 | 5 | 1.2 | 0.6994 | 1.29 | ( 0.35, 4.78) | 1.30 | ( 0.35, 4.86) | 0.00 | (-0.01, 0.02) | |
| Yes | 766 | 7 | 0.9 | 763 | 3 | 0.4 | 0.2066 | 0.43 | ( 0.11, 1.66) | 0.43 | ( 0.11, 1.66) | -0.01 | (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3978 |
| No | 629 | 5 | 0.8 | 589 | 5 | 0.8 | 0.9169 | 1.07 | ( 0.31, 3.67) | 1.07 | ( 0.31, 3.71) | 0.00 | (-0.01, 0.01) | |
| Yes | 559 | 6 | 1.1 | 582 | 3 | 0.5 | 0.2869 | 0.48 | ( 0.12, 1.91) | 0.48 | ( 0.12, 1.92) | -0.01 | (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 4 | 0.3 | 1171 | 4 | 0.3 | 0.9837 | 1.01 ( 0.25, 4.05) | 1.01 ( 0.25, 4.07) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 864 | 4 | 0.5 | 837 | 3 | 0.4 | | | | | |
| Female | 324 | 0 | 0 | 334 | 1 | 0.3 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 2 | 0.4 | 547 | 1 | 0.2 | | | | | |
| >=65 | 619 | 2 | 0.3 | 624 | 3 | 0.5 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 3 | 0.6 | 434 | 1 | 0.2 | | | | | |
| North America | 259 | 1 | 0.4 | 241 | 1 | 0.4 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 2 | 3.7 | | | | | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 1 | 0.2 | 566 | 1 | 0.2 | | | | | |
| >=30 | 634 | 3 | 0.5 | 605 | 3 | 0.5 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 2 | 0.5 | 382 | 0 | 0 | | | | | |
| >=130 | 809 | 2 | 0.2 | 789 | 4 | 0.5 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 2 | 0.4 | 500 | 0 | 0 | | | | | |
| 75 to <85 | 427 | 2 | 0.5 | 417 | 3 | 0.7 | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 1 | 0.4 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 4 | 0.4 | 1031 | 3 | 0.3 | | | | | |
| Yes | 140 | 0 | 0 | 140 | 1 | 0.7 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 178 | 1 | 0.6 | | | | | |
| >=45 | 1009 | 4 | 0.4 | 993 | 3 | 0.3 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 1 | 0.4 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 2 | 0.3 | 645 | 3 | 0.5 | | | | | |
| Macroalbuminuria (>300) | 260 | 1 | 0.4 | 261 | 1 | 0.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 4 | 0.4 | 1001 | 2 | 0.2 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 2 | 1.2 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 1 | 0.5 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 3 | 0.3 | 960 | 4 | 0.4 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 1 | 0.2 | 408 | 2 | 0.5 | | | | | |
| Yes | 766 | 3 | 0.4 | 763 | 2 | 0.3 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 1 | 0.2 | 589 | 2 | 0.3 | | | | | |
| Yes | 559 | 3 | 0.5 | 582 | 2 | 0.3 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 24 | 2.0 | 1171 | 20 | 1.7 | 0.5751 | 0.85 | ( 0.47, 1.52) | 0.84 | ( 0.46, 1.53) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.8296 |
| Male | 864 | 14 | 1.6 | 837 | 12 | 1.4 | 0.7537 | 0.88 | ( 0.41, 1.90) | 0.88 | ( 0.41, 1.92) | 0.00 | (-0.01, 0.01) | |
| Female | 324 | 10 | 3.1 | 334 | 8 | 2.4 | 0.5868 | 0.78 | ( 0.31, 1.94) | 0.77 | ( 0.30, 1.98) | -0.01 | (-0.03, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.1764 |
| <65 | 569 | 11 | 1.9 | 547 | 5 | 0.9 | 0.1522 | 0.47 | ( 0.17, 1.35) | 0.47 | ( 0.16, 1.36) | -0.01 | (-0.02, 0.00) | |
| >=65 | 619 | 13 | 2.1 | 624 | 15 | 2.4 | 0.7183 | 1.14 | ( 0.55, 2.39) | 1.15 | ( 0.54, 2.43) | 0.00 | (-0.01, 0.02) | |
| Region | | | | | | | | | | | | | | 0.3954 |
| Europe | 468 | 7 | 1.5 | 434 | 9 | 2.1 | 0.5111 | 1.39 | ( 0.52, 3.69) | 1.39 | ( 0.51, 3.78) | 0.01 | (-0.01, 0.02) | |
| North America | 259 | 7 | 2.7 | 241 | 4 | 1.7 | 0.4269 | 0.61 | ( 0.18, 2.07) | 0.61 | ( 0.18, 2.10) | -0.01 | (-0.04, 0.02) | |
| Latin America | 177 | 4 | 2.3 | 191 | 0 | 0 | 0.0591 | 0.10 | (<0.01, 1.90) | 0.10 | (<0.01, 1.88) | -0.02 | (-0.05, 0.00) | |
| Africa | 50 | 1 | 2.0 | 54 | 0 | 0 | 0.4423 | 0.31 | ( 0.01, 7.42) | 0.30 | ( 0.01, 7.61) | -0.02 | (-0.07, 0.03) | |
| Asia | 234 | 5 | 2.1 | 251 | 7 | 2.8 | 0.6441 | 1.31 | ( 0.42, 4.06) | 1.31 | ( 0.41, 4.20) | 0.01 | (-0.02, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6549 |
| <30 | 554 | 12 | 2.2 | 566 | 9 | 1.6 | 0.4774 | 0.73 | ( 0.31, 1.73) | 0.73 | ( 0.31, 1.75) | -0.01 | (-0.02, 0.01) | |
| >=30 | 634 | 12 | 1.9 | 605 | 11 | 1.8 | 0.9226 | 0.96 | ( 0.43, 2.16) | 0.96 | ( 0.42, 2.19) | 0.00 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1554 |
| <130 | 379 | 8 | 2.1 | 382 | 3 | 0.8 | 0.1256 | 0.37 | ( 0.10, 1.39) | 0.37 | ( 0.10, 1.39) | -0.01 | (-0.03, 0.00) | |
| >=130 | 809 | 16 | 2.0 | 789 | 17 | 2.2 | 0.8037 | 1.09 | ( 0.55, 2.14) | 1.09 | ( 0.55, 2.18) | 0.00 | (-0.01, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3683 |
| <75 | 500 | 9 | 1.8 | 500 | 10 | 2.0 | 0.8168 | 1.11 | ( 0.46, 2.71) | 1.11 | ( 0.45, 2.76) | 0.00 | (-0.01, 0.02) | |
| 75 to <85 | 427 | 11 | 2.6 | 417 | 5 | 1.2 | 0.1425 | 0.47 | ( 0.16, 1.33) | 0.46 | ( 0.16, 1.33) | -0.01 | (-0.03, 0.00) | |
| >=85 | 261 | 4 | 1.5 | 254 | 5 | 2.0 | 0.7058 | 1.28 | ( 0.35, 4.73) | 1.29 | ( 0.34, 4.86) | 0.00 | (-0.02, 0.03) | |
| History of heart failure | | | | | | | | | | | | | | 0.3940 |
| No | 1048 | 21 | 2.0 | 1031 | 19 | 1.8 | 0.7894 | 0.92 | ( 0.50, 1.70) | 0.92 | ( 0.49, 1.72) | 0.00 | (-0.01, 0.01) | |
| Yes | 140 | 3 | 2.1 | 140 | 1 | 0.7 | 0.3138 | 0.33 | ( 0.04, 3.17) | 0.33 | ( 0.03, 3.20) | -0.01 | (-0.04, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7507 |
| <45 | 179 | 5 | 2.8 | 178 | 5 | 2.8 | 0.9928 | 1.01 | ( 0.30, 3.41) | 1.01 | ( 0.29, 3.54) | 0.00 | (-0.03, 0.03) | |
| >=45 | 1009 | 19 | 1.9 | 993 | 15 | 1.5 | 0.5190 | 0.80 | ( 0.41, 1.57) | 0.80 | ( 0.40, 1.58) | 0.00 | (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5868 |
| Normal (<30) | 250 | 5 | 2.0 | 257 | 2 | 0.8 | 0.2385 | 0.39 | ( 0.08, 1.99) | 0.38 | ( 0.07, 2.00) | -0.01 | (-0.03, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 14 | 2.1 | 645 | 13 | 2.0 | 0.9401 | 0.97 | ( 0.46, 2.05) | 0.97 | ( 0.45, 2.08) | 0.00 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 260 | 5 | 1.9 | 261 | 5 | 1.9 | 0.9951 | 1.00 | ( 0.29, 3.40) | 1.00 | ( 0.28, 3.48) | 0.00 | (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9843 |
| Low, moderate or high | 1018 | 18 | 1.8 | 1001 | 15 | 1.5 | 0.6328 | 0.85 | ( 0.43, 1.67) | 0.85 | ( 0.42, 1.69) | 0.00 | (-0.01, 0.01) | |
| Very high | 167 | 6 | 3.6 | 162 | 5 | 3.1 | 0.7984 | 0.86 | ( 0.27, 2.76) | 0.85 | ( 0.26, 2.86) | -0.01 | (-0.04, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4366 |
| No | 205 | 7 | 3.4 | 211 | 4 | 1.9 | 0.3344 | 0.56 | ( 0.17, 1.87) | 0.55 | ( 0.16, 1.90) | -0.02 | (-0.05, 0.02) | |
| Yes | 983 | 17 | 1.7 | 960 | 16 | 1.7 | 0.9148 | 0.96 | ( 0.49, 1.90) | 0.96 | ( 0.48, 1.92) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6104 |
| No | 422 | 8 | 1.9 | 408 | 8 | 2.0 | 0.9457 | 1.03 | ( 0.39, 2.73) | 1.04 | ( 0.38, 2.78) | 0.00 | (-0.02, 0.02) | |
| Yes | 766 | 16 | 2.1 | 763 | 12 | 1.6 | 0.4518 | 0.75 | ( 0.36, 1.58) | 0.75 | ( 0.35, 1.59) | -0.01 | (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5063 |
| No | 629 | 15 | 2.4 | 589 | 10 | 1.7 | 0.3981 | 0.71 | ( 0.32, 1.57) | 0.71 | ( 0.32, 1.59) | -0.01 | (-0.02, 0.01) | |
| Yes | 559 | 9 | 1.6 | 582 | 10 | 1.7 | 0.8865 | 1.07 | ( 0.44, 2.61) | 1.07 | ( 0.43, 2.65) | 0.00 | (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 21 | 1.8 | 1171 | 16 | 1.4 | 0.4328 | 0.77 | ( 0.41, 1.47) | 0.77 | ( 0.40, 1.48) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.8612 |
| Male | 864 | 14 | 1.6 | 837 | 10 | 1.2 | 0.4568 | 0.74 | ( 0.33, 1.65) | 0.73 | ( 0.32, 1.66) | 0.00 | (-0.02, 0.01) | |
| Female | 324 | 7 | 2.2 | 334 | 6 | 1.8 | 0.7372 | 0.83 | ( 0.28, 2.45) | 0.83 | ( 0.28, 2.49) | 0.00 | (-0.02, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.2303 |
| <65 | 569 | 8 | 1.4 | 547 | 3 | 0.5 | 0.1472 | 0.39 | ( 0.10, 1.46) | 0.39 | ( 0.10, 1.47) | -0.01 | (-0.02, 0.00) | |
| >=65 | 619 | 13 | 2.1 | 624 | 13 | 2.1 | 0.9835 | 0.99 | ( 0.46, 2.12) | 0.99 | ( 0.46, 2.16) | 0.00 | (-0.02, 0.02) | |
| Region | | | | | | | | | | | | | | 0.9269 |
| Europe | 468 | 9 | 1.9 | 434 | 7 | 1.6 | 0.7244 | 0.84 | ( 0.32, 2.23) | 0.84 | ( 0.31, 2.26) | 0.00 | (-0.02, 0.01) | |
| North America | 259 | 9 | 3.5 | 241 | 6 | 2.5 | 0.5187 | 0.72 | ( 0.26, 1.98) | 0.71 | ( 0.25, 2.02) | -0.01 | (-0.04, 0.02) | |
| Latin America | 177 | 1 | 0.6 | 191 | 2 | 1.0 | 0.6073 | 1.85 | ( 0.17, 20.26) | 1.86 | ( 0.17, 20.72) | 0.00 | (-0.01, 0.02) | |
| Africa | 50 | 1 | 2.0 | 54 | 0 | 0 | 0.4423 | 0.31 | ( 0.01, 7.42) | 0.30 | ( 0.01, 7.61) | -0.02 | (-0.07, 0.03) | |
| Asia | 234 | 1 | 0.4 | 251 | 1 | 0.4 | 0.9604 | 0.93 | ( 0.06, 14.82) | 0.93 | ( 0.06, 14.99) | 0.00 | (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6311 |
| <30 | 554 | 6 | 1.1 | 566 | 6 | 1.1 | 0.9702 | 0.98 | ( 0.32, 3.02) | 0.98 | ( 0.31, 3.05) | 0.00 | (-0.01, 0.01) | |
| >=30 | 634 | 15 | 2.4 | 605 | 10 | 1.7 | 0.3723 | 0.70 | ( 0.32, 1.54) | 0.69 | ( 0.31, 1.56) | -0.01 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2916 |
| <130 | 379 | 10 | 2.6 | 382 | 5 | 1.3 | 0.1871 | 0.50 | ( 0.17, 1.44) | 0.49 | ( 0.17, 1.45) | -0.01 | (-0.03, 0.01) | |
| >=130 | 809 | 11 | 1.4 | 789 | 11 | 1.4 | 0.9529 | 1.03 | ( 0.45, 2.35) | 1.03 | ( 0.44, 2.38) | 0.00 | (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4253 |
| <75 | 500 | 12 | 2.4 | 500 | 7 | 1.4 | 0.2468 | 0.58 | ( 0.23, 1.47) | 0.58 | ( 0.23, 1.48) | -0.01 | (-0.03, 0.01) | |
| 75 to <85 | 427 | 5 | 1.2 | 417 | 7 | 1.7 | 0.5334 | 1.43 | ( 0.46, 4.48) | 1.44 | ( 0.45, 4.58) | 0.01 | (-0.01, 0.02) | |
| >=85 | 261 | 4 | 1.5 | 254 | 2 | 0.8 | 0.4308 | 0.51 | ( 0.09, 2.78) | 0.51 | ( 0.09, 2.81) | -0.01 | (-0.03, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.6249 |
| No | 1048 | 16 | 1.5 | 1031 | 11 | 1.1 | 0.3545 | 0.70 | ( 0.33, 1.50) | 0.70 | ( 0.32, 1.51) | 0.00 | (-0.01, 0.01) | |
| Yes | 140 | 5 | 3.6 | 140 | 5 | 3.6 | 1.0000 | 1.00 | ( 0.30, 3.38) | 1.00 | ( 0.28, 3.53) | 0.00 | (-0.04, 0.04) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0721 |
| <45 | 179 | 7 | 3.9 | 178 | 1 | 0.6 | 0.0326 | 0.14 | ( 0.02, 1.16) | 0.14 | ( 0.02, 1.14) | -0.03 | (-0.06, 0.00) | |
| >=45 | 1009 | 14 | 1.4 | 993 | 15 | 1.5 | 0.8178 | 1.09 | ( 0.53, 2.24) | 1.09 | ( 0.52, 2.27) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1327 |
| Normal (<30) | 250 | 10 | 4.0 | 257 | 3 | 1.2 | 0.0436 | 0.29 | ( 0.08, 1.05) | 0.28 | ( 0.08, 1.04) | -0.03 | (-0.06, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 8 | 1.2 | 645 | 6 | 0.9 | 0.6513 | 0.78 | ( 0.27, 2.25) | 0.78 | ( 0.27, 2.27) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 260 | 3 | 1.2 | 261 | 6 | 2.3 | 0.3159 | 1.99 | ( 0.50, 7.88) | 2.02 | ( 0.50, 8.15) | 0.01 | (-0.01, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3481 |
| Low, moderate or high | 1018 | 18 | 1.8 | 1001 | 11 | 1.1 | 0.2063 | 0.62 | ( 0.30, 1.31) | 0.62 | ( 0.29, 1.31) | -0.01 | (-0.02, 0.00) | |
| Very high | 167 | 3 | 1.8 | 162 | 4 | 2.5 | 0.6725 | 1.37 | ( 0.31, 6.05) | 1.38 | ( 0.30, 6.28) | 0.01 | (-0.02, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2198 |
| No | 205 | 1 | 0.5 | 211 | 3 | 1.4 | 0.3291 | 2.91 | ( 0.31, 27.79) | 2.94 | ( 0.30, 28.52) | 0.01 | (-0.01, 0.03) | |
| Yes | 983 | 20 | 2.0 | 960 | 13 | 1.4 | 0.2458 | 0.67 | ( 0.33, 1.33) | 0.66 | ( 0.33, 1.34) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8986 |
| No | 422 | 3 | 0.7 | 408 | 2 | 0.5 | 0.6812 | 0.69 | ( 0.12, 4.11) | 0.69 | ( 0.11, 4.14) | 0.00 | (-0.01, 0.01) | |
| Yes | 766 | 18 | 2.3 | 763 | 14 | 1.8 | 0.4818 | 0.78 | ( 0.39, 1.56) | 0.78 | ( 0.38, 1.57) | -0.01 | (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1386 |
| No | 629 | 6 | 1.0 | 589 | 8 | 1.4 | 0.5082 | 1.42 | ( 0.50, 4.08) | 1.43 | ( 0.49, 4.15) | 0.00 | (-0.01, 0.02) | |
| Yes | 559 | 15 | 2.7 | 582 | 8 | 1.4 | 0.1158 | 0.51 | ( 0.22, 1.20) | 0.51 | ( 0.21, 1.20) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 45 | 3.8 | 1171 | 30 | 2.6 | 0.0897 | 0.68 | ( 0.43, | 1.07) | 0.67 | ( 0.42, | 1.07) | -0.01 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.6119 |
| Male | 864 | 33 | 3.8 | 837 | 20 | 2.4 | 0.0897 | 0.63 | ( 0.36, | 1.08) | 0.62 | ( 0.35, | 1.08) | -0.01 | (-0.03, 0.00) | |
| Female | 324 | 12 | 3.7 | 334 | 10 | 3.0 | 0.6127 | 0.81 | ( 0.35, | 1.84) | 0.80 | ( 0.34, | 1.88) | -0.01 | (-0.03, 0.02) | |
| Age [years] | | | | | | | | | | | | | | | | 0.8317 |
| <65 | 569 | 15 | 2.6 | 547 | 9 | 1.6 | 0.2540 | 0.62 | ( 0.28, | 1.41) | 0.62 | ( 0.27, | 1.42) | -0.01 | (-0.03, 0.01) | |
| >=65 | 619 | 30 | 4.8 | 624 | 21 | 3.4 | 0.1881 | 0.69 | ( 0.40, | 1.20) | 0.68 | ( 0.39, | 1.21) | -0.01 | (-0.04, 0.01) | |
| Region | | | | | | | | | | | | | | | | 0.6059 |
| Europe | 468 | 13 | 2.8 | 434 | 9 | 2.1 | 0.4934 | 0.75 | ( 0.32, | 1.73) | 0.74 | ( 0.31, | 1.75) | -0.01 | (-0.03, 0.01) | |
| North America | 259 | 16 | 6.2 | 241 | 12 | 5.0 | 0.5603 | 0.81 | ( 0.39, | 1.67) | 0.80 | ( 0.37, | 1.72) | -0.01 | (-0.05, 0.03) | |
| Latin America | 177 | 2 | 1.1 | 191 | 3 | 1.6 | 0.7152 | 1.39 | ( 0.24, | 8.22) | 1.40 | ( 0.23, | 8.46) | 0.00 | (-0.02, 0.03) | |
| Africa | 50 | 4 | 8.0 | 54 | 3 | 5.6 | 0.6191 | 0.69 | ( 0.16, | 2.95) | 0.68 | ( 0.14, | 3.18) | -0.02 | (-0.12, 0.07) | |
| Asia | 234 | 10 | 4.3 | 251 | 3 | 1.2 | 0.0360 | 0.28 | ( 0.08, | >1.00) | 0.27 | ( 0.07, | 1.00) | -0.03 | (-0.06, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.8086 |
| <30 | 554 | 20 | 3.6 | 566 | 13 | 2.3 | 0.1938 | 0.64 | ( 0.32, | 1.27) | 0.63 | ( 0.31, | 1.27) | -0.01 | (-0.03, 0.01) | |
| >=30 | 634 | 25 | 3.9 | 605 | 17 | 2.8 | 0.2705 | 0.71 | ( 0.39, | 1.31) | 0.70 | ( 0.38, | 1.32) | -0.01 | (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.6407 |
| <130 | 379 | 17 | 4.5 | 382 | 10 | 2.6 | 0.1637 | 0.58 | ( 0.27, | 1.26) | 0.57 | ( 0.26, | 1.27) | -0.02 | (-0.04, 0.01) | |
| >=130 | 809 | 28 | 3.5 | 789 | 20 | 2.5 | 0.2781 | 0.73 | ( 0.42, | 1.29) | 0.73 | ( 0.41, | 1.30) | -0.01 | (-0.03, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.3476 |
| <75 | 500 | 21 | 4.2 | 500 | 13 | 2.6 | 0.1627 | 0.62 | ( 0.31, | 1.22) | 0.61 | ( 0.30, | 1.23) | -0.02 | (-0.04, 0.01) | |
| 75 to <85 | 427 | 19 | 4.4 | 417 | 10 | 2.4 | 0.1019 | 0.54 | ( 0.25, | 1.15) | 0.53 | ( 0.24, | 1.15) | -0.02 | (-0.04, 0.00) | |
| >=85 | 261 | 5 | 1.9 | 254 | 7 | 2.8 | 0.5275 | 1.44 | ( 0.46, | 4.47) | 1.45 | ( 0.45, | 4.63) | 0.01 | (-0.02, 0.03) | |
| History of heart failure | | | | | | | | | | | | | | | | 0.8608 |
| No | 1048 | 31 | 3.0 | 1031 | 20 | 1.9 | 0.1335 | 0.66 | ( 0.38, | 1.14) | 0.65 | ( 0.37, | 1.15) | -0.01 | (-0.02, 0.00) | |
| Yes | 140 | 14 | 10.0 | 140 | 10 | 7.1 | 0.3932 | 0.71 | ( 0.33, | 1.55) | 0.69 | ( 0.30, | 1.62) | -0.03 | (-0.09, 0.04) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
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User-defined AE category: Acute renal failure (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.7250 |
| <45 | 179 | 12 | 6.7 | 178 | 7 | 3.9 | 0.2435 | 0.59 ( 0.24, 1.46) | 0.57 ( 0.22, 1.48) | -0.03 (-0.07, 0.02) | |
| >=45 | 1009 | 33 | 3.3 | 993 | 23 | 2.3 | 0.1954 | 0.71 ( 0.42, 1.20) | 0.70 ( 0.41, 1.20) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.7584 |
| Normal (<30) | 250 | 15 | 6.0 | 257 | 8 | 3.1 | 0.1183 | 0.52 ( 0.22, 1.20) | 0.50 ( 0.21, 1.21) | -0.03 (-0.07, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 16 | 2.4 | 645 | 12 | 1.9 | 0.5204 | 0.78 ( 0.37, 1.65) | 0.78 ( 0.37, 1.66) | -0.01 (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 260 | 14 | 5.4 | 261 | 10 | 3.8 | 0.3978 | 0.71 ( 0.32, 1.57) | 0.70 ( 0.31, 1.61) | -0.02 (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.9792 |
| Low, moderate or high | 1018 | 33 | 3.2 | 1001 | 22 | 2.2 | 0.1497 | 0.68 ( 0.40, 1.15) | 0.67 ( 0.39, 1.16) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 12 | 7.2 | 162 | 8 | 4.9 | 0.3937 | 0.69 ( 0.29, 1.64) | 0.67 ( 0.27, 1.69) | -0.02 (-0.07, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.6106 |
| No | 205 | 6 | 2.9 | 211 | 3 | 1.4 | 0.2915 | 0.49 ( 0.12, 1.92) | 0.48 ( 0.12, 1.94) | -0.02 (-0.04, 0.01) | |
| Yes | 983 | 39 | 4.0 | 960 | 27 | 2.8 | 0.1600 | 0.71 ( 0.44, 1.15) | 0.70 ( 0.43, 1.15) | -0.01 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.0792 |
| No | 422 | 18 | 4.3 | 408 | 6 | 1.5 | 0.0163 | 0.34 ( 0.14, 0.86) | 0.33 ( 0.13, 0.85) | -0.03 (-0.05,-0.01) | |
| Yes | 766 | 27 | 3.5 | 763 | 24 | 3.1 | 0.6796 | 0.89 ( 0.52, 1.53) | 0.89 ( 0.51, 1.55) | 0.00 (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9639 |
| No | 629 | 8 | 1.3 | 589 | 5 | 0.8 | 0.4728 | 0.67 ( 0.22, 2.03) | 0.66 ( 0.22, 2.04) | 0.00 (-0.02, 0.01) | |
| Yes | 559 | 37 | 6.6 | 582 | 25 | 4.3 | 0.0835 | 0.65 ( 0.40, 1.06) | 0.63 ( 0.38, 1.07) | -0.02 (-0.05, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 0 | 0 | 1171 | 0 | 0 | | | | | |
| Sex | | | | | | | | | | | |
| Male | 864 | 0 | 0 | 837 | 0 | 0 | | | | | |
| Female | 324 | 0 | 0 | 334 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 0 | 0 | 547 | 0 | 0 | | | | | |
| >=65 | 619 | 0 | 0 | 624 | 0 | 0 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 0 | 0 | 434 | 0 | 0 | | | | | |
| North America | 259 | 0 | 0 | 241 | 0 | 0 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 0 | 0 | 566 | 0 | 0 | | | | | |
| >=30 | 634 | 0 | 0 | 605 | 0 | 0 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 382 | 0 | 0 | | | | | |
| >=130 | 809 | 0 | 0 | 789 | 0 | 0 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 0 | 0 | 500 | 0 | 0 | | | | | |
| 75 to <85 | 427 | 0 | 0 | 417 | 0 | 0 | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 0 | 0 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 0 | 0 | 1031 | 0 | 0 | | | | | |
| Yes | 140 | 0 | 0 | 140 | 0 | 0 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 178 | 0 | 0 | | | | | |
| >=45 | 1009 | 0 | 0 | 993 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 0 | 0 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 0 | 0 | 645 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 0 | 0 | 1001 | 0 | 0 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 0 | 0 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 0 | 0 | 960 | 0 | 0 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 0 | 0 | 408 | 0 | 0 | | | | | |
| Yes | 766 | 0 | 0 | 763 | 0 | 0 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 0 | 0 | 589 | 0 | 0 | | | | | |
| Yes | 559 | 0 | 0 | 582 | 0 | 0 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 4 | 0.3 | 1171 | 2 | 0.2 | 0.4238 | 0.51 ( 0.09, 2.76) | 0.51 ( 0.09, 2.77) | 0.00 (-0.01, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 864 | 4 | 0.5 | 837 | 2 | 0.2 | | | | | |
| Female | 324 | 0 | 0 | 334 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 2 | 0.4 | 547 | 0 | 0 | | | | | |
| >=65 | 619 | 2 | 0.3 | 624 | 2 | 0.3 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 3 | 0.6 | 434 | 1 | 0.2 | | | | | |
| North America | 259 | 1 | 0.4 | 241 | 0 | 0 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 1 | 1.9 | | | | | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 0 | 0 | 566 | 2 | 0.4 | | | | | |
| >=30 | 634 | 4 | 0.6 | 605 | 0 | 0 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 382 | 0 | 0 | | | | | |
| >=130 | 809 | 4 | 0.5 | 789 | 2 | 0.3 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 2 | 0.4 | 500 | 1 | 0.2 | | | | | |
| 75 to <85 | 427 | 0 | 0 | 417 | 0 | 0 | | | | | |
| >=85 | 261 | 2 | 0.8 | 254 | 1 | 0.4 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 4 | 0.4 | 1031 | 1 | 0.1 | | | | | |
| Yes | 140 | 0 | 0 | 140 | 1 | 0.7 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 1 | 0.6 | 178 | 1 | 0.6 | | | | | |
| >=45 | 1009 | 3 | 0.3 | 993 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 2 | 0.8 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 0 | 0 | 645 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 260 | 2 | 0.8 | 261 | 1 | 0.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 4 | 0.4 | 1001 | 1 | 0.1 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 1 | 0.6 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 1 | 0.5 | 211 | 1 | 0.5 | | | | | |
| Yes | 983 | 3 | 0.3 | 960 | 1 | 0.1 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 2 | 0.5 | 408 | 1 | 0.2 | | | | | |
| Yes | 766 | 2 | 0.3 | 763 | 1 | 0.1 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 1 | 0.2 | 589 | 0 | 0 | | | | | |
| Yes | 559 | 3 | 0.5 | 582 | 2 | 0.3 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: $Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 5 | 0.4 | 0.0941 | 0.42 | ( 0.15, 1.20) | 0.42 | ( 0.15, 1.20) | -0.01 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | |
| Male | 864 | 8 | 0.9 | 837 | 1 | 0.1 | | | | | | | | |
| Female | 324 | 4 | 1.2 | 334 | 4 | 1.2 | | | | | | | | |
| Age [years] | | | | | | | | | | | | | | 0.9841 |
| <65 | 569 | 5 | 0.9 | 547 | 2 | 0.4 | 0.2778 | 0.42 | ( 0.08, 2.14) | 0.41 | ( 0.08, 2.14) | -0.01 | (-0.01, 0.00) | |
| >=65 | 619 | 7 | 1.1 | 624 | 3 | 0.5 | 0.1996 | 0.43 | ( 0.11, 1.64) | 0.42 | ( 0.11, 1.64) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | |
| Europe | 468 | 3 | 0.6 | 434 | 0 | 0 | | | | | | | | |
| North America | 259 | 4 | 1.5 | 241 | 1 | 0.4 | | | | | | | | |
| Latin America | 177 | 1 | 0.6 | 191 | 2 | 1.0 | | | | | | | | |
| Africa | 50 | 1 | 2.0 | 54 | 0 | 0 | | | | | | | | |
| Asia | 234 | 3 | 1.3 | 251 | 2 | 0.8 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4357 |
| <30 | 554 | 7 | 1.3 | 566 | 4 | 0.7 | 0.3448 | 0.56 | ( 0.16, 1.90) | 0.56 | ( 0.16, 1.91) | -0.01 | (-0.02, 0.01) | |
| >=30 | 634 | 5 | 0.8 | 605 | 1 | 0.2 | 0.1141 | 0.21 | ( 0.02, 1.79) | 0.21 | ( 0.02, 1.79) | -0.01 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5217 |
| <130 | 379 | 1 | 0.3 | 382 | 1 | 0.3 | 0.9955 | 0.99 | ( 0.06, 15.80) | 0.99 | ( 0.06, 15.92) | 0.00 | (-0.01, 0.01) | |
| >=130 | 809 | 11 | 1.4 | 789 | 4 | 0.5 | 0.0772 | 0.37 | ( 0.12, 1.17) | 0.37 | ( 0.12, 1.17) | -0.01 | (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6045 |
| <75 | 500 | 8 | 1.6 | 500 | 3 | 0.6 | 0.1295 | 0.38 | ( 0.10, 1.41) | 0.37 | ( 0.10, 1.41) | -0.01 | (-0.02, 0.00) | |
| 75 to <85 | 427 | 2 | 0.5 | 417 | 2 | 0.5 | 0.9810 | 1.02 | ( 0.14, 7.24) | 1.02 | ( 0.14, 7.30) | 0.00 | (-0.01, 0.01) | |
| >=85 | 261 | 2 | 0.8 | 254 | 0 | 0 | 0.2565 | 0.21 | (<0.01, 4.26) | 0.20 | (<0.01, 4.27) | -0.01 | (-0.02, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.8490 |
| No | 1048 | 11 | 1.0 | 1031 | 5 | 0.5 | 0.1407 | 0.46 | ( 0.16, 1.33) | 0.46 | ( 0.16, 1.33) | -0.01 | (-0.01, 0.00) | |
| Yes | 140 | 1 | 0.7 | 140 | 0 | 0 | 0.4779 | 0.33 | ( 0.01, 8.11) | 0.33 | ( 0.01, 8.19) | -0.01 | (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: $Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9567 |
| <45 | 179 | 7 | 3.9 | 178 | 3 | 1.7 | 0.2027 | 0.43 | ( 0.11, 1.64) | 0.42 | ( 0.11, 1.66) | -0.02 | (-0.06, 0.01) | |
| >=45 | 1009 | 5 | 0.5 | 993 | 2 | 0.2 | 0.2650 | 0.41 | ( 0.08, 2.09) | 0.41 | ( 0.08, 2.09) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | |
| Normal (<30) | 250 | 4 | 1.6 | 257 | 0 | 0 | | | | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 5 | 0.7 | 645 | 2 | 0.3 | | | | | | | | |
| Macroalbuminuria (>300) | 260 | 3 | 1.2 | 261 | 3 | 1.1 | | | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | |
| Low, moderate or high | 1018 | 8 | 0.8 | 1001 | 1 | 0.1 | | | | | | | | |
| Very high | 167 | 4 | 2.4 | 162 | 4 | 2.5 | | | | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6905 |
| No | 205 | 0 | 0 | 211 | 0 | 0 | 0.9885 | 0.97 | ( 0.02, 48.74) | 0.97 | ( 0.02, 49.20) | 0.00 | (-0.01, 0.01) | |
| Yes | 983 | 12 | 1.2 | 960 | 5 | 0.5 | 0.0977 | 0.43 | ( 0.15, 1.21) | 0.42 | ( 0.15, 1.21) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6020 |
| No | 422 | 4 | 0.9 | 408 | 1 | 0.2 | 0.1909 | 0.26 | ( 0.03, 2.30) | 0.26 | ( 0.03, 2.31) | -0.01 | (-0.02, 0.00) | |
| Yes | 766 | 8 | 1.0 | 763 | 4 | 0.5 | 0.2491 | 0.50 | ( 0.15, 1.66) | 0.50 | ( 0.15, 1.67) | -0.01 | (-0.01, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2718 |
| No | 629 | 4 | 0.6 | 589 | 3 | 0.5 | 0.7702 | 0.80 | ( 0.18, 3.56) | 0.80 | ( 0.18, 3.59) | 0.00 | (-0.01, 0.01) | |
| Yes | 559 | 8 | 1.4 | 582 | 2 | 0.3 | 0.0488 | 0.24 | ( 0.05, 1.13) | 0.24 | ( 0.05, 1.12) | -0.01 | (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Seriousness criteria of events was not assessed, therefore no serious Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Lower Limb Amputations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 0 | 0 | 1171 | 0 | 0 | | | | | |
| Sex | | | | | | | | | | | |
| Male | 864 | 0 | 0 | 837 | 0 | 0 | | | | | |
| Female | 324 | 0 | 0 | 334 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 0 | 0 | 547 | 0 | 0 | | | | | |
| >=65 | 619 | 0 | 0 | 624 | 0 | 0 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 0 | 0 | 434 | 0 | 0 | | | | | |
| North America | 259 | 0 | 0 | 241 | 0 | 0 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 0 | 0 | 566 | 0 | 0 | | | | | |
| >=30 | 634 | 0 | 0 | 605 | 0 | 0 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 382 | 0 | 0 | | | | | |
| >=130 | 809 | 0 | 0 | 789 | 0 | 0 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 0 | 0 | 500 | 0 | 0 | | | | | |
| 75 to <85 | 427 | 0 | 0 | 417 | 0 | 0 | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 0 | 0 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 0 | 0 | 1031 | 0 | 0 | | | | | |
| Yes | 140 | 0 | 0 | 140 | 0 | 0 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Lower Limb Amputations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 178 | 0 | 0 | | | | | |
| >=45 | 1009 | 0 | 0 | 993 | 0 | 0 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 0 | 0 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 0 | 0 | 645 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 0 | 0 | 1001 | 0 | 0 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 0 | 0 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 0 | 0 | 960 | 0 | 0 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 0 | 0 | 408 | 0 | 0 | | | | | |
| Yes | 766 | 0 | 0 | 763 | 0 | 0 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 0 | 0 | 589 | 0 | 0 | | | | | |
| Yes | 559 | 0 | 0 | 582 | 0 | 0 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 1 | 0.1 | 1171 | 3 | 0.3 | 0.3100 | 3.04 ( 0.32,29.22) | 3.05 ( 0.32,29.35) | 0.00 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | |
| Male | 864 | 1 | 0.1 | 837 | 1 | 0.1 | | | | | |
| Female | 324 | 0 | 0 | 334 | 2 | 0.6 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 1 | 0.2 | 547 | 0 | 0 | | | | | |
| >=65 | 619 | 0 | 0 | 624 | 3 | 0.5 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 1 | 0.2 | 434 | 1 | 0.2 | | | | | |
| North America | 259 | 0 | 0 | 241 | 1 | 0.4 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 1 | 0.5 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 0 | 0 | 566 | 1 | 0.2 | | | | | |
| >=30 | 634 | 1 | 0.2 | 605 | 2 | 0.3 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 382 | 0 | 0 | | | | | |
| >=130 | 809 | 1 | 0.1 | 789 | 3 | 0.4 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 0 | 0 | 500 | 1 | 0.2 | | | | | |
| 75 to <85 | 427 | 1 | 0.2 | 417 | 2 | 0.5 | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 0 | 0 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 1 | 0.1 | 1031 | 2 | 0.2 | | | | | |
| Yes | 140 | 0 | 0 | 140 | 1 | 0.7 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 178 | 0 | 0 | | | | | |
| >=45 | 1009 | 1 | 0.1 | 993 | 3 | 0.3 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 0 | 0 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 1 | 0.1 | 645 | 2 | 0.3 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 1 | 0.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 1 | 0.1 | 1001 | 2 | 0.2 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 1 | 0.6 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 0 | 0 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 1 | 0.1 | 960 | 3 | 0.3 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 0 | 0 | 408 | 1 | 0.2 | | | | | |
| Yes | 766 | 1 | 0.1 | 763 | 2 | 0.3 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 0 | 0 | 589 | 2 | 0.3 | | | | | |
| Yes | 559 | 1 | 0.2 | 582 | 1 | 0.2 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** | |
| Overall | 1188 | 0 | 0 | 1171 | 1 | 0.1 | 0.4730 | 3.04 ( 0.12,74.63) | 3.05 ( 0.12,74.85) | 0.00 ( 0.00, 0.00) | | |
| Sex | | | | | | | | | | | | |
| Male | 864 | 0 | 0 | 837 | 1 | 0.1 | | | | | | |
| Female | 324 | 0 | 0 | 334 | 0 | 0 | | | | | | |
| Age [years] | | | | | | | | | | | | |
| <65 | 569 | 0 | 0 | 547 | 0 | 0 | | | | | | |
| >=65 | 619 | 0 | 0 | 624 | 1 | 0.2 | | | | | | |
| Region | | | | | | | | | | | | |
| Europe | 468 | 0 | 0 | 434 | 0 | 0 | | | | | | |
| North America | 259 | 0 | 0 | 241 | 0 | 0 | | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | | |
| Africa | 50 | 0 | 0 | 54 | 1 | 1.9 | | | | | | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | |
| <30 | 554 | 0 | 0 | 566 | 1 | 0.2 | | | | | | |
| >=30 | 634 | 0 | 0 | 605 | 0 | 0 | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 382 | 0 | 0 | | | | | | |
| >=130 | 809 | 0 | 0 | 789 | 1 | 0.1 | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 500 | 0 | 0 | 500 | 0 | 0 | | | | | | |
| 75 to <85 | 427 | 0 | 0 | 417 | 0 | 0 | | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 1 | 0.4 | | | | | | |
| History of heart failure | | | | | | | | | | | | |
| No | 1048 | 0 | 0 | 1031 | 1 | 0.1 | | | | | | |
| Yes | 140 | 0 | 0 | 140 | 0 | 0 | | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 178 | 0 | 0 | | | | | |
| >=45 | 1009 | 0 | 0 | 993 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 0 | 0 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 0 | 0 | 645 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 0 | 0 | 1001 | 1 | 0.1 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 0 | 0 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 0 | 0 | 960 | 1 | 0.1 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 0 | 0 | 408 | 0 | 0 | | | | | |
| Yes | 766 | 0 | 0 | 763 | 1 | 0.1 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 0 | 0 | 589 | 0 | 0 | | | | | |
| Yes | 559 | 0 | 0 | 582 | 1 | 0.2 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 32 | 2.7 | 1171 | 22 | 1.9 | 0.1858 | 0.70 | ( 0.41, 1.19) | 0.69 | ( 0.40, 1.20) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.1983 |
| Male | 864 | 22 | 2.5 | 837 | 11 | 1.3 | 0.0655 | 0.52 | ( 0.25, 1.06) | 0.51 | ( 0.25, 1.06) | -0.01 | (-0.03, 0.00) | |
| Female | 324 | 10 | 3.1 | 334 | 11 | 3.3 | 0.8800 | 1.07 | ( 0.46, 2.48) | 1.07 | ( 0.45, 2.55) | 0.00 | (-0.02, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.8326 |
| <65 | 569 | 14 | 2.5 | 547 | 10 | 1.8 | 0.4667 | 0.74 | ( 0.33, 1.66) | 0.74 | ( 0.33, 1.68) | -0.01 | (-0.02, 0.01) | |
| >=65 | 619 | 18 | 2.9 | 624 | 12 | 1.9 | 0.2580 | 0.66 | ( 0.32, 1.36) | 0.65 | ( 0.31, 1.37) | -0.01 | (-0.03, 0.01) | |
| Region | | | | | | | | | | | | | | 0.8260 |
| Europe | 468 | 7 | 1.5 | 434 | 3 | 0.7 | 0.2489 | 0.46 | ( 0.12, 1.78) | 0.46 | ( 0.12, 1.78) | -0.01 | (-0.02, 0.01) | |
| North America | 259 | 12 | 4.6 | 241 | 6 | 2.5 | 0.1986 | 0.54 | ( 0.20, 1.41) | 0.53 | ( 0.19, 1.42) | -0.02 | (-0.05, 0.01) | |
| Latin America | 177 | 4 | 2.3 | 191 | 5 | 2.6 | 0.8242 | 1.16 | ( 0.32, 4.25) | 1.16 | ( 0.31, 4.40) | 0.00 | (-0.03, 0.04) | |
| Africa | 50 | 3 | 6.0 | 54 | 2 | 3.7 | 0.5844 | 0.62 | ( 0.11, 3.54) | 0.60 | ( 0.10, 3.76) | -0.02 | (-0.11, 0.06) | |
| Asia | 234 | 6 | 2.6 | 251 | 6 | 2.4 | 0.9021 | 0.93 | ( 0.30, 2.85) | 0.93 | ( 0.30, 2.93) | 0.00 | (-0.03, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7063 |
| <30 | 554 | 20 | 3.6 | 566 | 13 | 2.3 | 0.1938 | 0.64 | ( 0.32, 1.27) | 0.63 | ( 0.31, 1.27) | -0.01 | (-0.03, 0.01) | |
| >=30 | 634 | 12 | 1.9 | 605 | 9 | 1.5 | 0.5808 | 0.79 | ( 0.33, 1.85) | 0.78 | ( 0.33, 1.87) | 0.00 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7346 |
| <130 | 379 | 10 | 2.6 | 382 | 8 | 2.1 | 0.6213 | 0.79 | ( 0.32, 1.99) | 0.79 | ( 0.31, 2.02) | -0.01 | (-0.03, 0.02) | |
| >=130 | 809 | 22 | 2.7 | 789 | 14 | 1.8 | 0.2031 | 0.65 | ( 0.34, 1.27) | 0.65 | ( 0.33, 1.27) | -0.01 | (-0.02, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8339 |
| <75 | 500 | 20 | 4.0 | 500 | 14 | 2.8 | 0.2951 | 0.70 | ( 0.36, 1.37) | 0.69 | ( 0.35, 1.38) | -0.01 | (-0.03, 0.01) | |
| 75 to <85 | 427 | 9 | 2.1 | 417 | 5 | 1.2 | 0.3014 | 0.57 | ( 0.19, 1.68) | 0.56 | ( 0.19, 1.70) | -0.01 | (-0.03, 0.01) | |
| >=85 | 261 | 3 | 1.1 | 254 | 3 | 1.2 | 0.9733 | 1.03 | ( 0.21, 5.04) | 1.03 | ( 0.21, 5.14) | 0.00 | (-0.02, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.5030 |
| No | 1048 | 29 | 2.8 | 1031 | 21 | 2.0 | 0.2772 | 0.74 | ( 0.42, 1.28) | 0.73 | ( 0.41, 1.29) | -0.01 | (-0.02, 0.01) | |
| Yes | 140 | 3 | 2.1 | 140 | 1 | 0.7 | 0.3138 | 0.33 | ( 0.04, 3.17) | 0.33 | ( 0.03, 3.20) | -0.01 | (-0.04, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4911 |
| <45 | 179 | 13 | 7.3 | 178 | 7 | 3.9 | 0.1713 | 0.54 | ( 0.22, 1.33) | 0.52 | ( 0.20, 1.34) | -0.03 | (-0.08, 0.01) | |
| >=45 | 1009 | 19 | 1.9 | 993 | 15 | 1.5 | 0.5190 | 0.80 | ( 0.41, 1.57) | 0.80 | ( 0.40, 1.58) | 0.00 | (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4011 |
| Normal (<30) | 250 | 8 | 3.2 | 257 | 4 | 1.6 | 0.2236 | 0.49 | ( 0.15, 1.59) | 0.48 | ( 0.14, 1.61) | -0.02 | (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 12 | 1.8 | 645 | 12 | 1.9 | 0.9105 | 1.05 | ( 0.47, 2.31) | 1.05 | ( 0.47, 2.35) | 0.00 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 260 | 12 | 4.6 | 261 | 6 | 2.3 | 0.1477 | 0.50 | ( 0.19, 1.31) | 0.49 | ( 0.18, 1.32) | -0.02 | (-0.05, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3811 |
| Low, moderate or high | 1018 | 18 | 1.8 | 1001 | 15 | 1.5 | 0.6328 | 0.85 | ( 0.43, 1.67) | 0.85 | ( 0.42, 1.69) | 0.00 | (-0.01, 0.01) | |
| Very high | 167 | 14 | 8.4 | 162 | 7 | 4.3 | 0.1318 | 0.52 | ( 0.21, 1.24) | 0.49 | ( 0.19, 1.26) | -0.04 | (-0.09, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7332 |
| No | 205 | 2 | 1.0 | 211 | 2 | 0.9 | 0.9769 | 0.97 | ( 0.14, 6.83) | 0.97 | ( 0.14, 6.96) | 0.00 | (-0.02, 0.02) | |
| Yes | 983 | 30 | 3.1 | 960 | 20 | 2.1 | 0.1776 | 0.68 | ( 0.39, 1.19) | 0.68 | ( 0.38, 1.20) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7302 |
| No | 422 | 9 | 2.1 | 408 | 7 | 1.7 | 0.6622 | 0.80 | ( 0.30, 2.14) | 0.80 | ( 0.30, 2.17) | 0.00 | (-0.02, 0.01) | |
| Yes | 766 | 23 | 3.0 | 763 | 15 | 2.0 | 0.1929 | 0.65 | ( 0.34, 1.25) | 0.65 | ( 0.34, 1.25) | -0.01 | (-0.03, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9198 |
| No | 629 | 12 | 1.9 | 589 | 8 | 1.4 | 0.4507 | 0.71 | ( 0.29, 1.73) | 0.71 | ( 0.29, 1.74) | -0.01 | (-0.02, 0.01) | |
| Yes | 559 | 20 | 3.6 | 582 | 14 | 2.4 | 0.2443 | 0.67 | ( 0.34, 1.32) | 0.66 | ( 0.33, 1.33) | -0.01 | (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 13 | 1.1 | 1171 | 11 | 0.9 | 0.7078 | 0.86 | ( 0.39, 1.91) | 0.86 | ( 0.38, 1.92) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.1147 |
| Male | 864 | 8 | 0.9 | 837 | 3 | 0.4 | 0.1443 | 0.39 | ( 0.10, 1.45) | 0.38 | ( 0.10, 1.46) | -0.01 | (-0.01, 0.00) | |
| Female | 324 | 5 | 1.5 | 334 | 8 | 2.4 | 0.4324 | 1.55 | ( 0.51, 4.69) | 1.57 | ( 0.51, 4.84) | 0.01 | (-0.01, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.8041 |
| <65 | 569 | 3 | 0.5 | 547 | 2 | 0.4 | 0.6861 | 0.69 | ( 0.12, 4.13) | 0.69 | ( 0.12, 4.16) | 0.00 | (-0.01, 0.01) | |
| >=65 | 619 | 10 | 1.6 | 624 | 9 | 1.4 | 0.8035 | 0.89 | ( 0.37, 2.18) | 0.89 | ( 0.36, 2.21) | 0.00 | (-0.02, 0.01) | |
| Region | | | | | | | | | | | | | | |
| Europe | 468 | 5 | 1.1 | 434 | 3 | 0.7 | | | | | | | | |
| North America | 259 | 5 | 1.9 | 241 | 3 | 1.2 | | | | | | | | |
| Latin America | 177 | 1 | 0.6 | 191 | 2 | 1.0 | | | | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | | | | |
| Asia | 234 | 2 | 0.9 | 251 | 3 | 1.2 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9062 |
| <30 | 554 | 6 | 1.1 | 566 | 5 | 0.9 | 0.7348 | 0.82 | ( 0.25, 2.66) | 0.81 | ( 0.25, 2.68) | 0.00 | (-0.01, 0.01) | |
| >=30 | 634 | 7 | 1.1 | 605 | 6 | 1.0 | 0.8462 | 0.90 | ( 0.30, 2.66) | 0.90 | ( 0.30, 2.69) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3242 |
| <130 | 379 | 6 | 1.6 | 382 | 3 | 0.8 | 0.3087 | 0.50 | ( 0.12, 1.97) | 0.49 | ( 0.12, 1.98) | -0.01 | (-0.02, 0.01) | |
| >=130 | 809 | 7 | 0.9 | 789 | 8 | 1.0 | 0.7580 | 1.17 | ( 0.43, 3.22) | 1.17 | ( 0.42, 3.25) | 0.00 | (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9260 |
| <75 | 500 | 6 | 1.2 | 500 | 6 | 1.2 | 1.0000 | 1.00 | ( 0.32, 3.08) | 1.00 | ( 0.32, 3.12) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 427 | 4 | 0.9 | 417 | 3 | 0.7 | 0.7278 | 0.77 | ( 0.17, 3.41) | 0.77 | ( 0.17, 3.44) | 0.00 | (-0.01, 0.01) | |
| >=85 | 261 | 3 | 1.1 | 254 | 2 | 0.8 | 0.6753 | 0.69 | ( 0.12, 4.07) | 0.68 | ( 0.11, 4.12) | 0.00 | (-0.02, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.0766 |
| No | 1048 | 8 | 0.8 | 1031 | 11 | 1.1 | 0.4671 | 1.40 | ( 0.56, 3.46) | 1.40 | ( 0.56, 3.50) | 0.00 | (-0.01, 0.01) | |
| Yes | 140 | 5 | 3.6 | 140 | 0 | 0 | 0.0391 | 0.09 | (<0.01, 1.63) | 0.09 | (<0.01, 1.60) | -0.04 | (-0.07, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2494 |
| <45 | 179 | 2 | 1.1 | 178 | 4 | 2.2 | 0.4063 | 2.01 | ( 0.37,10.84) | 2.03 | ( 0.37,11.25) | 0.01 | (-0.02, 0.04) | |
| >=45 | 1009 | 11 | 1.1 | 993 | 7 | 0.7 | 0.3612 | 0.65 | ( 0.25, 1.66) | 0.64 | ( 0.25, 1.67) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1222 |
| Normal (<30) | 250 | 3 | 1.2 | 257 | 0 | 0 | 0.1251 | 0.14 | (<0.01, 2.68) | 0.14 | (<0.01, 2.67) | -0.01 | (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 9 | 1.3 | 645 | 6 | 0.9 | 0.4898 | 0.70 | ( 0.25, 1.95) | 0.69 | ( 0.25, 1.96) | 0.00 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 260 | 1 | 0.4 | 261 | 5 | 1.9 | 0.1015 | 4.98 | ( 0.59,42.34) | 5.06 | ( 0.59,43.60) | 0.02 | ( 0.00, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0532 |
| Low, moderate or high | 1018 | 12 | 1.2 | 1001 | 6 | 0.6 | 0.1661 | 0.51 | ( 0.19, 1.35) | 0.51 | ( 0.19, 1.35) | -0.01 | (-0.01, 0.00) | |
| Very high | 167 | 1 | 0.6 | 162 | 5 | 3.1 | 0.0918 | 5.15 | ( 0.61,43.64) | 5.29 | ( 0.61,45.75) | 0.02 | ( 0.00, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3507 |
| No | 205 | 3 | 1.5 | 211 | 1 | 0.5 | 0.3012 | 0.32 | ( 0.03, 3.09) | 0.32 | ( 0.03, 3.11) | -0.01 | (-0.03, 0.01) | |
| Yes | 983 | 10 | 1.0 | 960 | 10 | 1.0 | 0.9576 | 1.02 | ( 0.43, 2.45) | 1.02 | ( 0.42, 2.47) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7449 |
| No | 422 | 4 | 0.9 | 408 | 4 | 1.0 | 0.9618 | 1.03 | ( 0.26, 4.11) | 1.03 | ( 0.26, 4.16) | 0.00 | (-0.01, 0.01) | |
| Yes | 766 | 9 | 1.2 | 763 | 7 | 0.9 | 0.6208 | 0.78 | ( 0.29, 2.09) | 0.78 | ( 0.29, 2.10) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6793 |
| No | 629 | 4 | 0.6 | 589 | 4 | 0.7 | 0.9257 | 1.07 | ( 0.27, 4.25) | 1.07 | ( 0.27, 4.29) | 0.00 | (-0.01, 0.01) | |
| Yes | 559 | 9 | 1.6 | 582 | 7 | 1.2 | 0.5586 | 0.75 | ( 0.28, 1.99) | 0.74 | ( 0.28, 2.01) | 0.00 | (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pylenophritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 6 | 0.5 | 1171 | 6 | 0.5 | 0.9800 | 1.01 | ( 0.33, 3.14) | 1.01 | ( 0.33, 3.15) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | |
| Male | 864 | 5 | 0.6 | 837 | 2 | 0.2 | | | | | | | | |
| Female | 324 | 1 | 0.3 | 334 | 4 | 1.2 | | | | | | | | |
| Age [years] | | | | | | | | | | | | | | 0.9755 |
| <65 | 569 | 1 | 0.2 | 547 | 1 | 0.2 | 0.9777 | 1.04 | ( 0.07,16.59) | 1.04 | ( 0.06,16.67) | 0.00 | ( 0.00, 0.01) | |
| >=65 | 619 | 5 | 0.8 | 624 | 5 | 0.8 | 0.9898 | 0.99 | ( 0.29, 3.41) | 0.99 | ( 0.29, 3.44) | 0.00 | (-0.01, 0.01) | |
| Region | | | | | | | | | | | | | | |
| Europe | 468 | 2 | 0.4 | 434 | 2 | 0.5 | | | | | | | | |
| North America | 259 | 2 | 0.8 | 241 | 1 | 0.4 | | | | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 1 | 0.5 | | | | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | | | | |
| Asia | 234 | 2 | 0.9 | 251 | 2 | 0.8 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | |
| <30 | 554 | 3 | 0.5 | 566 | 3 | 0.5 | | | | | | | | |
| >=30 | 634 | 3 | 0.5 | 605 | 3 | 0.5 | | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | |
| <130 | 379 | 2 | 0.5 | 382 | 2 | 0.5 | | | | | | | | |
| >=130 | 809 | 4 | 0.5 | 789 | 4 | 0.5 | | | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | |
| <75 | 500 | 3 | 0.6 | 500 | 3 | 0.6 | | | | | | | | |
| 75 to <85 | 427 | 2 | 0.5 | 417 | 1 | 0.2 | | | | | | | | |
| >=85 | 261 | 1 | 0.4 | 254 | 2 | 0.8 | | | | | | | | |
| History of heart failure | | | | | | | | | | | | | | 0.4552 |
| No | 1048 | 5 | 0.5 | 1031 | 6 | 0.6 | 0.7418 | 1.22 | ( 0.37, 3.98) | 1.22 | ( 0.37, 4.01) | 0.00 | (-0.01, 0.01) | |
| Yes | 140 | 1 | 0.7 | 140 | 0 | 0 | 0.4779 | 0.33 | ( 0.01, 8.11) | 0.33 | ( 0.01, 8.19) | -0.01 | (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
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User-defined AE category: Pylenophritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 2 | 1.1 | 178 | 2 | 1.1 | | | | | |
| >=45 | 1009 | 4 | 0.4 | 993 | 4 | 0.4 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 2 | 0.8 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 3 | 0.4 | 645 | 3 | 0.5 | | | | | |
| Macroalbuminuria (>300) | 260 | 1 | 0.4 | 261 | 3 | 1.1 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 5 | 0.5 | 1001 | 3 | 0.3 | | | | | |
| Very high | 167 | 1 | 0.6 | 162 | 3 | 1.9 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.2171 |
| No | 205 | 2 | 1.0 | 211 | 0 | 0 | 0.2364 | 0.19 (<0.01, 4.02) | 0.19 (<0.01, 4.03) | -0.01 (-0.03, 0.01) | |
| Yes | 983 | 4 | 0.4 | 960 | 6 | 0.6 | 0.5018 | 1.54 ( 0.43, 5.43) | 1.54 ( 0.43, 5.47) | 0.00 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 2 | 0.5 | 408 | 4 | 1.0 | | | | | |
| Yes | 766 | 4 | 0.5 | 763 | 2 | 0.3 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 3 | 0.5 | 589 | 2 | 0.3 | | | | | |
| Yes | 559 | 3 | 0.5 | 582 | 4 | 0.7 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
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MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 2 | 0.2 | 1171 | 2 | 0.2 | 0.9885 | 1.01 ( 0.14, 7.19) | 1.01 ( 0.14, 7.21) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 864 | 1 | 0.1 | 837 | 1 | 0.1 | | | | | |
| Female | 324 | 1 | 0.3 | 334 | 1 | 0.3 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 0 | 0 | 547 | 0 | 0 | | | | | |
| >=65 | 619 | 2 | 0.3 | 624 | 2 | 0.3 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 1 | 0.2 | 434 | 0 | 0 | | | | | |
| North America | 259 | 1 | 0.4 | 241 | 1 | 0.4 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 1 | 1.9 | | | | | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 0 | 0 | 566 | 1 | 0.2 | | | | | |
| >=30 | 634 | 2 | 0.3 | 605 | 1 | 0.2 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 2 | 0.5 | 382 | 0 | 0 | | | | | |
| >=130 | 809 | 0 | 0 | 789 | 2 | 0.3 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 1 | 0.2 | 500 | 0 | 0 | | | | | |
| 75 to <85 | 427 | 1 | 0.2 | 417 | 2 | 0.5 | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 0 | 0 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 1 | 0.1 | 1031 | 2 | 0.2 | | | | | |
| Yes | 140 | 1 | 0.7 | 140 | 0 | 0 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
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MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 178 | 1 | 0.6 | | | | | |
| >=45 | 1009 | 2 | 0.2 | 993 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 1 | 0.4 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 1 | 0.1 | 645 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 1 | 0.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 2 | 0.2 | 1001 | 0 | 0 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 2 | 1.2 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 1 | 0.5 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 1 | 0.1 | 960 | 2 | 0.2 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 0 | 0 | 408 | 1 | 0.2 | | | | | |
| Yes | 766 | 2 | 0.3 | 763 | 1 | 0.1 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 0 | 0 | 589 | 1 | 0.2 | | | | | |
| Yes | 559 | 2 | 0.4 | 582 | 1 | 0.2 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 10 | 0.8 | 1171 | 12 | 1.0 | 0.6438 | 1.22 | ( 0.53, 2.81) | 1.22 | ( 0.52, 2.83) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.7489 |
| Male | 864 | 5 | 0.6 | 837 | 5 | 0.6 | 0.9598 | 1.03 | ( 0.30, 3.55) | 1.03 | ( 0.30, 3.58) | 0.00 | (-0.01, 0.01) | |
| Female | 324 | 5 | 1.5 | 334 | 7 | 2.1 | 0.5964 | 1.36 | ( 0.44, 4.24) | 1.37 | ( 0.43, 4.35) | 0.01 | (-0.01, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.1170 |
| <65 | 569 | 5 | 0.9 | 547 | 2 | 0.4 | 0.2778 | 0.42 | ( 0.08, 2.14) | 0.41 | ( 0.08, 2.14) | -0.01 | (-0.01, 0.00) | |
| >=65 | 619 | 5 | 0.8 | 624 | 10 | 1.6 | 0.1994 | 1.98 | ( 0.68, 5.77) | 2.00 | ( 0.68, 5.89) | 0.01 | ( 0.00, 0.02) | |
| Region | | | | | | | | | | | | | | |
| Europe | 468 | 2 | 0.4 | 434 | 5 | 1.2 | | | | | | | | |
| North America | 259 | 4 | 1.5 | 241 | 4 | 1.7 | | | | | | | | |
| Latin America | 177 | 2 | 1.1 | 191 | 0 | 0 | | | | | | | | |
| Africa | 50 | 1 | 2.0 | 54 | 0 | 0 | | | | | | | | |
| Asia | 234 | 1 | 0.4 | 251 | 3 | 1.2 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7382 |
| <30 | 554 | 3 | 0.5 | 566 | 3 | 0.5 | 0.9790 | 0.98 | ( 0.20, 4.83) | 0.98 | ( 0.20, 4.87) | 0.00 | (-0.01, 0.01) | |
| >=30 | 634 | 7 | 1.1 | 605 | 9 | 1.5 | 0.5501 | 1.35 | ( 0.50, 3.60) | 1.35 | ( 0.50, 3.65) | 0.00 | (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0982 |
| <130 | 379 | 4 | 1.1 | 382 | 1 | 0.3 | 0.1754 | 0.25 | ( 0.03, 2.21) | 0.25 | ( 0.03, 2.21) | -0.01 | (-0.02, 0.00) | |
| >=130 | 809 | 6 | 0.7 | 789 | 11 | 1.4 | 0.2037 | 1.88 | ( 0.70, 5.06) | 1.89 | ( 0.70, 5.14) | 0.01 | ( 0.00, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | |
| <75 | 500 | 2 | 0.4 | 500 | 7 | 1.4 | | | | | | | | |
| 75 to <85 | 427 | 7 | 1.6 | 417 | 2 | 0.5 | | | | | | | | |
| >=85 | 261 | 1 | 0.4 | 254 | 3 | 1.2 | | | | | | | | |
| History of heart failure | | | | | | | | | | | | | | 0.4056 |
| No | 1048 | 9 | 0.9 | 1031 | 12 | 1.2 | 0.4866 | 1.36 | ( 0.57, 3.20) | 1.36 | ( 0.57, 3.24) | 0.00 | (-0.01, 0.01) | |
| Yes | 140 | 1 | 0.7 | 140 | 0 | 0 | 0.4779 | 0.33 | ( 0.01, 8.11) | 0.33 | ( 0.01, 8.19) | -0.01 | (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7355 |
| <45 | 179 | 4 | 2.2 | 178 | 4 | 2.2 | 0.9936 | 1.01 | ( 0.26, 3.96) | 1.01 | ( 0.25, 4.09) | 0.00 | (-0.03, 0.03) | |
| >=45 | 1009 | 6 | 0.6 | 993 | 8 | 0.8 | 0.5711 | 1.35 | ( 0.47, 3.89) | 1.36 | ( 0.47, 3.93) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9625 |
| Normal (<30) | 250 | 1 | 0.4 | 257 | 1 | 0.4 | 0.9844 | 0.97 | ( 0.06,15.47) | 0.97 | ( 0.06,15.64) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 7 | 1.0 | 645 | 8 | 1.2 | 0.7276 | 1.20 | ( 0.44, 3.28) | 1.20 | ( 0.43, 3.32) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 260 | 2 | 0.8 | 261 | 3 | 1.1 | 0.6563 | 1.49 | ( 0.25, 8.87) | 1.50 | ( 0.25, 9.05) | 0.00 | (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7559 |
| Low, moderate or high | 1018 | 6 | 0.6 | 1001 | 8 | 0.8 | 0.5700 | 1.36 | ( 0.47, 3.89) | 1.36 | ( 0.47, 3.93) | 0.00 | (-0.01, 0.01) | |
| Very high | 167 | 4 | 2.4 | 162 | 4 | 2.5 | 0.9653 | 1.03 | ( 0.26, 4.05) | 1.03 | ( 0.25, 4.20) | 0.00 | (-0.03, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9117 |
| No | 205 | 3 | 1.5 | 211 | 4 | 1.9 | 0.7318 | 1.30 | ( 0.29, 5.72) | 1.30 | ( 0.29, 5.89) | 0.00 | (-0.02, 0.03) | |
| Yes | 983 | 7 | 0.7 | 960 | 8 | 0.8 | 0.7602 | 1.17 | ( 0.43, 3.21) | 1.17 | ( 0.42, 3.24) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4490 |
| No | 422 | 5 | 1.2 | 408 | 4 | 1.0 | 0.7762 | 0.83 | ( 0.22, 3.06) | 0.83 | ( 0.22, 3.10) | 0.00 | (-0.02, 0.01) | |
| Yes | 766 | 5 | 0.7 | 763 | 8 | 1.0 | 0.3994 | 1.61 | ( 0.53, 4.89) | 1.61 | ( 0.53, 4.95) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4080 |
| No | 629 | 7 | 1.1 | 589 | 6 | 1.0 | 0.8730 | 0.92 | ( 0.31, 2.71) | 0.91 | ( 0.31, 2.74) | 0.00 | (-0.01, 0.01) | |
| Yes | 559 | 3 | 0.5 | 582 | 6 | 1.0 | 0.3455 | 1.92 | ( 0.48, 7.64) | 1.93 | ( 0.48, 7.76) | 0.00 | (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 13 | 1.1 | 1171 | 9 | 0.8 | 0.4106 | 0.70 | ( 0.30, 1.64) | 0.70 | ( 0.30, 1.64) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.2780 |
| Male | 864 | 9 | 1.0 | 837 | 4 | 0.5 | 0.1819 | 0.46 | ( 0.14, 1.48) | 0.46 | ( 0.14, 1.49) | -0.01 | (-0.01, 0.00) | |
| Female | 324 | 4 | 1.2 | 334 | 5 | 1.5 | 0.7720 | 1.21 | ( 0.33, 4.48) | 1.22 | ( 0.32, 4.57) | 0.00 | (-0.02, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.6929 |
| <65 | 569 | 4 | 0.7 | 547 | 2 | 0.4 | 0.4410 | 0.52 | ( 0.10, 2.83) | 0.52 | ( 0.09, 2.84) | 0.00 | (-0.01, 0.01) | |
| >=65 | 619 | 9 | 1.5 | 624 | 7 | 1.1 | 0.6034 | 0.77 | ( 0.29, 2.06) | 0.77 | ( 0.28, 2.08) | 0.00 | (-0.02, 0.01) | |
| Region | | | | | | | | | | | | | | 0.9189 |
| Europe | 468 | 5 | 1.1 | 434 | 5 | 1.2 | 0.9045 | 1.08 | ( 0.31, 3.70) | 1.08 | ( 0.31, 3.75) | 0.00 | (-0.01, 0.01) | |
| North America | 259 | 6 | 2.3 | 241 | 4 | 1.7 | 0.6001 | 0.72 | ( 0.20, 2.51) | 0.71 | ( 0.20, 2.55) | -0.01 | (-0.03, 0.02) | |
| Latin America | 177 | 1 | 0.6 | 191 | 0 | 0 | 0.4453 | 0.31 | ( 0.01, 7.54) | 0.31 | ( 0.01, 7.59) | -0.01 | (-0.02, 0.01) | |
| Africa | 50 | 1 | 2.0 | 54 | 0 | 0 | 0.4423 | 0.31 | ( 0.01, 7.42) | 0.30 | ( 0.01, 7.61) | -0.02 | (-0.07, 0.03) | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | 0.9721 | 0.93 | ( 0.02,46.81) | 0.93 | ( 0.02,47.18) | 0.00 | (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5624 |
| <30 | 554 | 4 | 0.7 | 566 | 4 | 0.7 | 0.9757 | 0.98 | ( 0.25, 3.89) | 0.98 | ( 0.24, 3.93) | 0.00 | (-0.01, 0.01) | |
| >=30 | 634 | 9 | 1.4 | 605 | 5 | 0.8 | 0.3235 | 0.58 | ( 0.20, 1.73) | 0.58 | ( 0.19, 1.74) | -0.01 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2443 |
| <130 | 379 | 6 | 1.6 | 382 | 2 | 0.5 | 0.1519 | 0.33 | ( 0.07, 1.63) | 0.33 | ( 0.07, 1.63) | -0.01 | (-0.03, 0.00) | |
| >=130 | 809 | 7 | 0.9 | 789 | 7 | 0.9 | 0.9625 | 1.03 | ( 0.36, 2.91) | 1.03 | ( 0.36, 2.94) | 0.00 | (-0.01, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4124 |
| <75 | 500 | 8 | 1.6 | 500 | 3 | 0.6 | 0.1295 | 0.38 | ( 0.10, 1.41) | 0.37 | ( 0.10, 1.41) | -0.01 | (-0.02, 0.00) | |
| 75 to <85 | 427 | 3 | 0.7 | 417 | 4 | 1.0 | 0.6810 | 1.37 | ( 0.31, 6.06) | 1.37 | ( 0.30, 6.15) | 0.00 | (-0.01, 0.01) | |
| >=85 | 261 | 2 | 0.8 | 254 | 2 | 0.8 | 0.9782 | 1.03 | ( 0.15, 7.24) | 1.03 | ( 0.14, 7.35) | 0.00 | (-0.01, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.9121 |
| No | 1048 | 9 | 0.9 | 1031 | 6 | 0.6 | 0.4559 | 0.68 | ( 0.24, 1.90) | 0.68 | ( 0.24, 1.91) | 0.00 | (-0.01, 0.00) | |
| Yes | 140 | 4 | 2.9 | 140 | 3 | 2.1 | 0.7019 | 0.75 | ( 0.17, 3.29) | 0.74 | ( 0.16, 3.39) | -0.01 | (-0.04, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
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MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1045 |
| <45 | 179 | 6 | 3.4 | 178 | 1 | 0.6 | 0.0573 | 0.17 | ( 0.02, 1.38) | 0.16 | ( 0.02, 1.37) | -0.03 | (-0.06, 0.00) | |
| >=45 | 1009 | 7 | 0.7 | 993 | 8 | 0.8 | 0.7716 | 1.16 | ( 0.42, 3.19) | 1.16 | ( 0.42, 3.22) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | |
| Normal (<30) | 250 | 7 | 2.8 | 257 | 1 | 0.4 | | | | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 5 | 0.7 | 645 | 4 | 0.6 | | | | | | | | |
| Macroalbuminuria (>300) | 260 | 1 | 0.4 | 261 | 3 | 1.1 | | | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2518 |
| Low, moderate or high | 1018 | 11 | 1.1 | 1001 | 5 | 0.5 | 0.1410 | 0.46 | ( 0.16, 1.33) | 0.46 | ( 0.16, 1.33) | -0.01 | (-0.01, 0.00) | |
| Very high | 167 | 2 | 1.2 | 162 | 3 | 1.9 | 0.6277 | 1.55 | ( 0.26, 9.13) | 1.56 | ( 0.26, 9.44) | 0.01 | (-0.02, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3676 |
| No | 205 | 1 | 0.5 | 211 | 2 | 0.9 | 0.5793 | 1.94 | ( 0.18,21.26) | 1.95 | ( 0.18,21.70) | 0.00 | (-0.01, 0.02) | |
| Yes | 983 | 12 | 1.2 | 960 | 7 | 0.7 | 0.2709 | 0.60 | ( 0.24, 1.51) | 0.59 | ( 0.23, 1.52) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9854 |
| No | 422 | 3 | 0.7 | 408 | 2 | 0.5 | 0.6812 | 0.69 | ( 0.12, 4.11) | 0.69 | ( 0.11, 4.14) | 0.00 | (-0.01, 0.01) | |
| Yes | 766 | 10 | 1.3 | 763 | 7 | 0.9 | 0.4693 | 0.70 | ( 0.27, 1.84) | 0.70 | ( 0.27, 1.85) | 0.00 | (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.0455 |
| No | 629 | 2 | 0.3 | 589 | 5 | 0.8 | 0.2206 | 2.67 | ( 0.52,13.71) | 2.68 | ( 0.52,13.89) | 0.01 | ( 0.00, 0.01) | |
| Yes | 559 | 11 | 2.0 | 582 | 4 | 0.7 | 0.0576 | 0.35 | ( 0.11, 1.09) | 0.34 | ( 0.11, 1.09) | -0.01 | (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 26 | 2.2 | 1171 | 17 | 1.5 | 0.1811 | 0.66 | ( 0.36, 1.22) | 0.66 | ( 0.36, 1.22) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0038 |
| Male | 864 | 24 | 2.8 | 837 | 8 | 1.0 | 0.0057 | 0.34 | ( 0.16, 0.76) | 0.34 | ( 0.15, 0.76) | -0.02 | (-0.03,-0.01) | |
| Female | 324 | 2 | 0.6 | 334 | 9 | 2.7 | 0.0377 | 4.37 | ( 0.95,20.05) | 4.46 | ( 0.96,20.79) | 0.02 | ( 0.00, 0.04) | |
| Age [years] | | | | | | | | | | | | | | 0.5210 |
| <65 | 569 | 7 | 1.2 | 547 | 3 | 0.5 | 0.2270 | 0.45 | ( 0.12, 1.72) | 0.44 | ( 0.11, 1.72) | -0.01 | (-0.02, 0.00) | |
| >=65 | 619 | 19 | 3.1 | 624 | 14 | 2.2 | 0.3651 | 0.73 | ( 0.37, 1.44) | 0.72 | ( 0.36, 1.46) | -0.01 | (-0.03, 0.01) | |
| Region | | | | | | | | | | | | | | 0.9485 |
| Europe | 468 | 9 | 1.9 | 434 | 6 | 1.4 | 0.5259 | 0.72 | ( 0.26, 2.00) | 0.71 | ( 0.25, 2.03) | -0.01 | (-0.02, 0.01) | |
| North America | 259 | 7 | 2.7 | 241 | 5 | 2.1 | 0.6466 | 0.77 | ( 0.25, 2.39) | 0.76 | ( 0.24, 2.44) | -0.01 | (-0.03, 0.02) | |
| Latin America | 177 | 3 | 1.7 | 191 | 2 | 1.0 | 0.5917 | 0.62 | ( 0.10, 3.65) | 0.61 | ( 0.10, 3.72) | -0.01 | (-0.03, 0.02) | |
| Africa | 50 | 5 | 10.0 | 54 | 2 | 3.7 | 0.2004 | 0.37 | ( 0.08, 1.82) | 0.35 | ( 0.06, 1.87) | -0.06 | (-0.16, 0.03) | |
| Asia | 234 | 2 | 0.9 | 251 | 2 | 0.8 | 0.9438 | 0.93 | ( 0.13, 6.56) | 0.93 | ( 0.13, 6.67) | 0.00 | (-0.02, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6501 |
| <30 | 554 | 10 | 1.8 | 566 | 8 | 1.4 | 0.6023 | 0.78 | ( 0.31, 1.97) | 0.78 | ( 0.31, 1.99) | 0.00 | (-0.02, 0.01) | |
| >=30 | 634 | 16 | 2.5 | 605 | 9 | 1.5 | 0.1948 | 0.59 | ( 0.26, 1.32) | 0.58 | ( 0.26, 1.33) | -0.01 | (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7665 |
| <130 | 379 | 7 | 1.8 | 382 | 4 | 1.0 | 0.3553 | 0.57 | ( 0.17, 1.92) | 0.56 | ( 0.16, 1.94) | -0.01 | (-0.02, 0.01) | |
| >=130 | 809 | 19 | 2.3 | 789 | 13 | 1.6 | 0.3173 | 0.70 | ( 0.35, 1.41) | 0.70 | ( 0.34, 1.42) | -0.01 | (-0.02, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8823 |
| <75 | 500 | 13 | 2.6 | 500 | 8 | 1.6 | 0.2701 | 0.62 | ( 0.26, 1.47) | 0.61 | ( 0.25, 1.48) | -0.01 | (-0.03, 0.01) | |
| 75 to <85 | 427 | 9 | 2.1 | 417 | 7 | 1.7 | 0.6477 | 0.80 | ( 0.30, 2.12) | 0.79 | ( 0.29, 2.15) | 0.00 | (-0.02, 0.01) | |
| >=85 | 261 | 4 | 1.5 | 254 | 2 | 0.8 | 0.4308 | 0.51 | ( 0.09, 2.78) | 0.51 | ( 0.09, 2.81) | -0.01 | (-0.03, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.7480 |
| No | 1048 | 21 | 2.0 | 1031 | 13 | 1.3 | 0.1818 | 0.63 | ( 0.32, 1.25) | 0.62 | ( 0.31, 1.25) | -0.01 | (-0.02, 0.00) | |
| Yes | 140 | 5 | 3.6 | 140 | 4 | 2.9 | 0.7347 | 0.80 | ( 0.22, 2.92) | 0.79 | ( 0.21, 3.02) | -0.01 | (-0.05, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1784 |
| <45 | 179 | 7 | 3.9 | 178 | 8 | 4.5 | 0.7834 | 1.15 | ( 0.43, 3.10) | 1.16 | ( 0.41, 3.26) | 0.01 | (-0.04, 0.05) | |
| >=45 | 1009 | 19 | 1.9 | 993 | 9 | 0.9 | 0.0628 | 0.48 | ( 0.22, 1.06) | 0.48 | ( 0.21, 1.06) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4307 |
| Normal (<30) | 250 | 7 | 2.8 | 257 | 2 | 0.8 | 0.0848 | 0.28 | ( 0.06, 1.33) | 0.27 | ( 0.06, 1.32) | -0.02 | (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 9 | 1.3 | 645 | 8 | 1.2 | 0.8809 | 0.93 | ( 0.36, 2.40) | 0.93 | ( 0.36, 2.42) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 260 | 10 | 3.8 | 261 | 7 | 2.7 | 0.4546 | 0.70 | ( 0.27, 1.80) | 0.69 | ( 0.26, 1.84) | -0.01 | (-0.04, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3321 |
| Low, moderate or high | 1018 | 16 | 1.6 | 1001 | 8 | 0.8 | 0.1093 | 0.51 | ( 0.22, 1.18) | 0.50 | ( 0.21, 1.18) | -0.01 | (-0.02, 0.00) | |
| Very high | 167 | 10 | 6.0 | 162 | 9 | 5.6 | 0.8665 | 0.93 | ( 0.39, 2.22) | 0.92 | ( 0.37, 2.34) | 0.00 | (-0.05, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6129 |
| No | 205 | 3 | 1.5 | 211 | 3 | 1.4 | 0.9716 | 0.97 | ( 0.20, 4.76) | 0.97 | ( 0.19, 4.87) | 0.00 | (-0.02, 0.02) | |
| Yes | 983 | 23 | 2.3 | 960 | 14 | 1.5 | 0.1552 | 0.62 | ( 0.32, 1.20) | 0.62 | ( 0.32, 1.21) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4635 |
| No | 422 | 9 | 2.1 | 408 | 4 | 1.0 | 0.1813 | 0.46 | ( 0.14, 1.48) | 0.45 | ( 0.14, 1.49) | -0.01 | (-0.03, 0.01) | |
| Yes | 766 | 17 | 2.2 | 763 | 13 | 1.7 | 0.4674 | 0.77 | ( 0.38, 1.57) | 0.76 | ( 0.37, 1.58) | -0.01 | (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1367 |
| No | 629 | 1 | 0.2 | 589 | 3 | 0.5 | 0.2855 | 3.20 | ( 0.33,30.71) | 3.22 | ( 0.33,30.99) | 0.00 | ( 0.00, 0.01) | |
| Yes | 559 | 25 | 4.5 | 582 | 14 | 2.4 | 0.0548 | 0.54 | ( 0.28, 1.02) | 0.53 | ( 0.27, 1.02) | -0.02 | (-0.04, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 1 | 0.1 | 1171 | 1 | 0.1 | 0.9919 | 1.01 ( 0.06,16.20) | 1.01 ( 0.06,16.24) | 0.00 ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | |
| Male | 864 | 1 | 0.1 | 837 | 1 | 0.1 | | | | | |
| Female | 324 | 0 | 0 | 334 | 0 | 0 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 0 | 0 | 547 | 0 | 0 | | | | | |
| >=65 | 619 | 1 | 0.2 | 624 | 1 | 0.2 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 0 | 0 | 434 | 1 | 0.2 | | | | | |
| North America | 259 | 0 | 0 | 241 | 0 | 0 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | |
| Asia | 234 | 1 | 0.4 | 251 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 554 | 1 | 0.2 | 566 | 0 | 0 | | | | | |
| >=30 | 634 | 0 | 0 | 605 | 1 | 0.2 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 382 | 0 | 0 | | | | | |
| >=130 | 809 | 1 | 0.1 | 789 | 1 | 0.1 | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 1 | 0.2 | 500 | 0 | 0 | | | | | |
| 75 to <85 | 427 | 0 | 0 | 417 | 1 | 0.2 | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 0 | 0 | | | | | |
| History of heart failure | | | | | | | | | | | |
| No | 1048 | 1 | 0.1 | 1031 | 1 | 0.1 | | | | | |
| Yes | 140 | 0 | 0 | 140 | 0 | 0 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 1 | 0.6 | 178 | 0 | 0 | | | | | |
| >=45 | 1009 | 0 | 0 | 993 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 0 | 0 | 257 | 1 | 0.4 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 0 | 0 | 645 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 260 | 1 | 0.4 | 261 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 0 | 0 | 1001 | 1 | 0.1 | | | | | |
| Very high | 167 | 1 | 0.6 | 162 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 1 | 0.5 | 211 | 0 | 0 | | | | | |
| Yes | 983 | 0 | 0 | 960 | 1 | 0.1 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 0 | 0 | 408 | 0 | 0 | | | | | |
| Yes | 766 | 1 | 0.1 | 763 | 1 | 0.1 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 0 | 0 | 589 | 0 | 0 | | | | | |
| Yes | 559 | 1 | 0.2 | 582 | 1 | 0.2 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** | |
| Overall | 1188 | 0 | 0 | 1171 | 1 | 0.1 | 0.4730 | 3.04 ( 0.12,74.63) | 3.05 ( 0.12,74.85) | 0.00 ( 0.00, 0.00) | | |
| Sex | | | | | | | | | | | | |
| Male | 864 | 0 | 0 | 837 | 1 | 0.1 | | | | | | |
| Female | 324 | 0 | 0 | 334 | 0 | 0 | | | | | | |
| Age [years] | | | | | | | | | | | | |
| <65 | 569 | 0 | 0 | 547 | 0 | 0 | | | | | | |
| >=65 | 619 | 0 | 0 | 624 | 1 | 0.2 | | | | | | |
| Region | | | | | | | | | | | | |
| Europe | 468 | 0 | 0 | 434 | 0 | 0 | | | | | | |
| North America | 259 | 0 | 0 | 241 | 0 | 0 | | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | | | | | | |
| Africa | 50 | 0 | 0 | 54 | 1 | 1.9 | | | | | | |
| Asia | 234 | 0 | 0 | 251 | 0 | 0 | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | |
| <30 | 554 | 0 | 0 | 566 | 1 | 0.2 | | | | | | |
| >=30 | 634 | 0 | 0 | 605 | 0 | 0 | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 379 | 0 | 0 | 382 | 0 | 0 | | | | | | |
| >=130 | 809 | 0 | 0 | 789 | 1 | 0.1 | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 500 | 0 | 0 | 500 | 1 | 0.2 | | | | | | |
| 75 to <85 | 427 | 0 | 0 | 417 | 0 | 0 | | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 0 | 0 | | | | | | |
| History of heart failure | | | | | | | | | | | | |
| No | 1048 | 0 | 0 | 1031 | 1 | 0.1 | | | | | | |
| Yes | 140 | 0 | 0 | 140 | 0 | 0 | | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <45 | 179 | 0 | 0 | 178 | 0 | 0 | | | | | |
| >=45 | 1009 | 0 | 0 | 993 | 1 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 0 | 0 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 0 | 0 | 645 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 0 | 0 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 1018 | 0 | 0 | 1001 | 1 | 0.1 | | | | | |
| Very high | 167 | 0 | 0 | 162 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 205 | 0 | 0 | 211 | 1 | 0.5 | | | | | |
| Yes | 983 | 0 | 0 | 960 | 0 | 0 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 0 | 0 | 408 | 1 | 0.2 | | | | | |
| Yes | 766 | 0 | 0 | 763 | 0 | 0 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 0 | 0 | 589 | 0 | 0 | | | | | |
| Yes | 559 | 0 | 0 | 582 | 1 | 0.2 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: $Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 28 | 2.4 | 1171 | 21 | 1.8 | 0.3373 | 0.76 | ( 0.43, 1.33) | 0.76 | ( 0.43, 1.34) | -0.01 | (-0.02, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.4592 |
| Male | 864 | 18 | 2.1 | 837 | 11 | 1.3 | 0.2206 | 0.63 | ( 0.30, 1.33) | 0.63 | ( 0.29, 1.33) | -0.01 | (-0.02, 0.00) | |
| Female | 324 | 10 | 3.1 | 334 | 10 | 3.0 | 0.9450 | 0.97 | ( 0.41, 2.30) | 0.97 | ( 0.40, 2.36) | 0.00 | (-0.03, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.7369 |
| <65 | 569 | 11 | 1.9 | 547 | 9 | 1.6 | 0.7171 | 0.85 | ( 0.36, 2.04) | 0.85 | ( 0.35, 2.06) | 0.00 | (-0.02, 0.01) | |
| >=65 | 619 | 17 | 2.7 | 624 | 12 | 1.9 | 0.3363 | 0.70 | ( 0.34, 1.45) | 0.69 | ( 0.33, 1.47) | -0.01 | (-0.03, 0.01) | |
| Region | | | | | | | | | | | | | | 0.8054 |
| Europe | 468 | 7 | 1.5 | 434 | 3 | 0.7 | 0.2489 | 0.46 | ( 0.12, 1.78) | 0.46 | ( 0.12, 1.78) | -0.01 | (-0.02, 0.01) | |
| North America | 259 | 10 | 3.9 | 241 | 6 | 2.5 | 0.3840 | 0.64 | ( 0.24, 1.75) | 0.64 | ( 0.23, 1.78) | -0.01 | (-0.04, 0.02) | |
| Latin America | 177 | 4 | 2.3 | 191 | 5 | 2.6 | 0.8242 | 1.16 | ( 0.32, 4.25) | 1.16 | ( 0.31, 4.40) | 0.00 | (-0.03, 0.04) | |
| Africa | 50 | 2 | 4.0 | 54 | 1 | 1.9 | 0.5131 | 0.46 | ( 0.04, 4.95) | 0.45 | ( 0.04, 5.15) | -0.02 | (-0.09, 0.04) | |
| Asia | 234 | 5 | 2.1 | 251 | 6 | 2.4 | 0.8513 | 1.12 | ( 0.35, 3.62) | 1.12 | ( 0.34, 3.73) | 0.00 | (-0.02, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7734 |
| <30 | 554 | 18 | 3.2 | 566 | 13 | 2.3 | 0.3314 | 0.71 | ( 0.35, 1.43) | 0.70 | ( 0.34, 1.44) | -0.01 | (-0.03, 0.01) | |
| >=30 | 634 | 10 | 1.6 | 605 | 8 | 1.3 | 0.7077 | 0.84 | ( 0.33, 2.11) | 0.84 | ( 0.33, 2.13) | 0.00 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3495 |
| <130 | 379 | 7 | 1.8 | 382 | 8 | 2.1 | 0.8062 | 1.13 | ( 0.42, 3.10) | 1.14 | ( 0.41, 3.17) | 0.00 | (-0.02, 0.02) | |
| >=130 | 809 | 21 | 2.6 | 789 | 13 | 1.6 | 0.1891 | 0.63 | ( 0.32, 1.26) | 0.63 | ( 0.31, 1.26) | -0.01 | (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6442 |
| <75 | 500 | 17 | 3.4 | 500 | 13 | 2.6 | 0.4584 | 0.76 | ( 0.38, 1.56) | 0.76 | ( 0.36, 1.58) | -0.01 | (-0.03, 0.01) | |
| 75 to <85 | 427 | 9 | 2.1 | 417 | 5 | 1.2 | 0.3014 | 0.57 | ( 0.19, 1.68) | 0.56 | ( 0.19, 1.70) | -0.01 | (-0.03, 0.01) | |
| >=85 | 261 | 2 | 0.8 | 254 | 3 | 1.2 | 0.6312 | 1.54 | ( 0.26, 9.15) | 1.55 | ( 0.26, 9.34) | 0.00 | (-0.01, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.4124 |
| No | 1048 | 27 | 2.6 | 1031 | 19 | 1.8 | 0.2556 | 0.72 | ( 0.40, 1.28) | 0.71 | ( 0.39, 1.29) | -0.01 | (-0.02, 0.01) | |
| Yes | 140 | 1 | 0.7 | 140 | 2 | 1.4 | 0.5616 | 2.00 | ( 0.18,21.81) | 2.01 | ( 0.18,22.47) | 0.01 | (-0.02, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: $Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4802 |
| <45 | 179 | 12 | 6.7 | 178 | 7 | 3.9 | 0.2435 | 0.59 | ( 0.24, 1.46) | 0.57 | ( 0.22, 1.48) | -0.03 | (-0.07, 0.02) | |
| >=45 | 1009 | 16 | 1.6 | 993 | 14 | 1.4 | 0.7461 | 0.89 | ( 0.44, 1.81) | 0.89 | ( 0.43, 1.83) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3081 |
| Normal (<30) | 250 | 8 | 3.2 | 257 | 4 | 1.6 | 0.2236 | 0.49 | ( 0.15, 1.59) | 0.48 | ( 0.14, 1.61) | -0.02 | (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 9 | 1.3 | 645 | 11 | 1.7 | 0.5801 | 1.28 | ( 0.53, 3.07) | 1.28 | ( 0.53, 3.12) | 0.00 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 260 | 11 | 4.2 | 261 | 6 | 2.3 | 0.2146 | 0.54 | ( 0.20, 1.45) | 0.53 | ( 0.19, 1.46) | -0.02 | (-0.05, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5052 |
| Low, moderate or high | 1018 | 16 | 1.6 | 1001 | 14 | 1.4 | 0.7479 | 0.89 | ( 0.44, 1.81) | 0.89 | ( 0.43, 1.83) | 0.00 | (-0.01, 0.01) | |
| Very high | 167 | 12 | 7.2 | 162 | 7 | 4.3 | 0.2655 | 0.60 | ( 0.24, 1.49) | 0.58 | ( 0.22, 1.52) | -0.03 | (-0.08, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4514 |
| No | 205 | 2 | 1.0 | 211 | 3 | 1.4 | 0.6763 | 1.46 | ( 0.25, 8.63) | 1.46 | ( 0.24, 8.85) | 0.00 | (-0.02, 0.03) | |
| Yes | 983 | 26 | 2.6 | 960 | 18 | 1.9 | 0.2540 | 0.71 | ( 0.39, 1.28) | 0.70 | ( 0.38, 1.29) | -0.01 | (-0.02, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8904 |
| No | 422 | 9 | 2.1 | 408 | 7 | 1.7 | 0.6622 | 0.80 | ( 0.30, 2.14) | 0.80 | ( 0.30, 2.17) | 0.00 | (-0.02, 0.01) | |
| Yes | 766 | 19 | 2.5 | 763 | 14 | 1.8 | 0.3851 | 0.74 | ( 0.37, 1.46) | 0.73 | ( 0.37, 1.48) | -0.01 | (-0.02, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9243 |
| No | 629 | 11 | 1.7 | 589 | 8 | 1.4 | 0.5825 | 0.78 | ( 0.31, 1.92) | 0.77 | ( 0.31, 1.94) | 0.00 | (-0.02, 0.01) | |
| Yes | 559 | 17 | 3.0 | 582 | 13 | 2.2 | 0.3941 | 0.73 | ( 0.36, 1.50) | 0.73 | ( 0.35, 1.51) | -0.01 | (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg. A continuity correction by 0.5 is applied in case of any zero cells in contingency table. For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
^Lower Limb Amputation events were identified post-hoc from a list of reported terms. Severity of events was not assessed, therefore no severe Lower Limb Amputation events are presented.
$Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.4.2.4**

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 739 | 62.2 | 1171 | 719 | 61.4 | 0.6875 | 0.99 ( 0.93, 1.05) | 0.97 ( 0.82, 1.14) | -0.01 | (-0.05, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 724 | 60.9 | 1171 | 636 | 54.3 | 0.0011 | 0.89 | ( 0.83, 0.96) | 0.76 | ( 0.65, 0.90) | -0.07 | (-0.11,-0.03) | |
| Sex | | | | | | | | | | | | | | 0.3021 |
| Male | 864 | 512 | 59.3 | 837 | 452 | 54.0 | 0.0287 | 0.91 | ( 0.84, 0.99) | 0.81 | ( 0.67, 0.98) | -0.05 | (-0.10,-0.01) | |
| Female | 324 | 212 | 65.4 | 334 | 184 | 55.1 | 0.0067 | 0.84 | ( 0.74, 0.95) | 0.65 | ( 0.47, 0.89) | -0.10 | (-0.18,-0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.1084 |
| <65 | 569 | 365 | 64.1 | 547 | 295 | 53.9 | 0.0005 | 0.84 | ( 0.76, 0.93) | 0.65 | ( 0.51, 0.83) | -0.10 | (-0.16,-0.04) | |
| >=65 | 619 | 359 | 58.0 | 624 | 341 | 54.6 | 0.2339 | 0.94 | ( 0.85, 1.04) | 0.87 | ( 0.70, 1.09) | -0.03 | (-0.09, 0.02) | |
| Region | | | | | | | | | | | | | | 0.9929 |
| Europe | 468 | 261 | 55.8 | 434 | 211 | 48.6 | 0.0317 | 0.87 | ( 0.77, 0.99) | 0.75 | ( 0.58, 0.98) | -0.07 | (-0.14,-0.01) | |
| North America | 259 | 158 | 61.0 | 241 | 133 | 55.2 | 0.1876 | 0.90 | ( 0.78, 1.05) | 0.79 | ( 0.55, 1.12) | -0.06 | (-0.14, 0.03) | |
| Latin America | 177 | 125 | 70.6 | 191 | 121 | 63.4 | 0.1388 | 0.90 | ( 0.78, 1.04) | 0.72 | ( 0.46, 1.11) | -0.07 | (-0.17, 0.02) | |
| Africa | 50 | 29 | 58.0 | 54 | 29 | 53.7 | 0.6594 | 0.93 | ( 0.66, 1.30) | 0.84 | ( 0.39, 1.82) | -0.04 | (-0.23, 0.15) | |
| Asia | 234 | 151 | 64.5 | 251 | 142 | 56.6 | 0.0734 | 0.88 | ( 0.76, 1.01) | 0.72 | ( 0.50, 1.03) | -0.08 | (-0.17, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6639 |
| <30 | 554 | 335 | 60.5 | 566 | 310 | 54.8 | 0.0537 | 0.91 | ( 0.82,>1.00) | 0.79 | ( 0.62, 1.00) | -0.06 | (-0.11, 0.00) | |
| >=30 | 634 | 389 | 61.4 | 605 | 326 | 53.9 | 0.0078 | 0.88 | ( 0.80, 0.97) | 0.74 | ( 0.59, 0.92) | -0.07 | (-0.13,-0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1487 |
| <130 | 379 | 232 | 61.2 | 382 | 193 | 50.5 | 0.0030 | 0.83 | ( 0.73, 0.94) | 0.65 | ( 0.49, 0.86) | -0.11 | (-0.18,-0.04) | |
| >=130 | 809 | 492 | 60.8 | 789 | 443 | 56.1 | 0.0582 | 0.92 | ( 0.85,>1.00) | 0.82 | ( 0.68, 1.01) | -0.05 | (-0.09, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2101 |
| <75 | 500 | 314 | 62.8 | 500 | 295 | 59.0 | 0.2182 | 0.94 | ( 0.85, 1.04) | 0.85 | ( 0.66, 1.10) | -0.04 | (-0.10, 0.02) | |
| 75 to <85 | 427 | 255 | 59.7 | 417 | 203 | 48.7 | 0.0013 | 0.82 | ( 0.72, 0.92) | 0.64 | ( 0.49, 0.84) | -0.11 | (-0.18,-0.04) | |
| >=85 | 261 | 155 | 59.4 | 254 | 138 | 54.3 | 0.2467 | 0.91 | ( 0.79, 1.06) | 0.81 | ( 0.57, 1.15) | -0.05 | (-0.14, 0.03) | |
| History of heart failure | | | | | | | | | | | | | | 0.8037 |
| No | 1048 | 634 | 60.5 | 1031 | 554 | 53.7 | 0.0018 | 0.89 | ( 0.82, 0.96) | 0.76 | ( 0.64, 0.90) | -0.07 | (-0.11,-0.03) | |
| Yes | 140 | 90 | 64.3 | 140 | 82 | 58.6 | 0.3260 | 0.91 | ( 0.76, 1.10) | 0.79 | ( 0.48, 1.27) | -0.06 | (-0.17, 0.06) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0841 |
| <45 | 179 | 112 | 62.6 | 178 | 113 | 63.5 | 0.8581 | 1.01 | ( 0.87, 1.19) | 1.04 | ( 0.68, 1.60) | 0.01 | (-0.09, 0.11) | |
| >=45 | 1009 | 612 | 60.7 | 993 | 523 | 52.7 | 0.0003 | 0.87 | ( 0.80, 0.94) | 0.72 | ( 0.60, 0.86) | -0.08 | (-0.12,-0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4766 |
| Normal (<30) | 250 | 140 | 56.0 | 257 | 138 | 53.7 | 0.6023 | 0.96 | ( 0.82, 1.12) | 0.91 | ( 0.64, 1.29) | -0.02 | (-0.11, 0.06) | |
| Microalbuminuria (30 to <=300) | 675 | 408 | 60.4 | 645 | 334 | 51.8 | 0.0015 | 0.86 | ( 0.78, 0.94) | 0.70 | ( 0.56, 0.87) | -0.09 | (-0.14,-0.03) | |
| Macroalbuminuria (>300) | 260 | 176 | 67.7 | 261 | 159 | 60.9 | 0.1067 | 0.90 | ( 0.79, 1.02) | 0.74 | ( 0.52, 1.07) | -0.07 | (-0.15, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9660 |
| Low, moderate or high | 1018 | 606 | 59.5 | 1001 | 529 | 52.8 | 0.0025 | 0.89 | ( 0.82, 0.96) | 0.76 | ( 0.64, 0.91) | -0.07 | (-0.11,-0.02) | |
| Very high | 167 | 118 | 70.7 | 162 | 102 | 63.0 | 0.1382 | 0.89 | ( 0.76, 1.04) | 0.71 | ( 0.45, 1.12) | -0.08 | (-0.18, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.0675 |
| No | 205 | 131 | 63.9 | 211 | 104 | 49.3 | 0.0026 | 0.77 | ( 0.65, 0.92) | 0.55 | ( 0.37, 0.81) | -0.15 | (-0.24,-0.05) | |
| Yes | 983 | 593 | 60.3 | 960 | 532 | 55.4 | 0.0284 | 0.92 | ( 0.85, 0.99) | 0.82 | ( 0.68, 0.98) | -0.05 | (-0.09,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.0964 |
| No | 422 | 261 | 61.8 | 408 | 207 | 50.7 | 0.0012 | 0.82 | ( 0.73, 0.93) | 0.64 | ( 0.48, 0.84) | -0.11 | (-0.18,-0.04) | |
| Yes | 766 | 463 | 60.4 | 763 | 429 | 56.2 | 0.0943 | 0.93 | ( 0.85, 1.01) | 0.84 | ( 0.69, 1.03) | -0.04 | (-0.09, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2462 |
| No | 629 | 379 | 60.3 | 589 | 303 | 51.4 | 0.0020 | 0.85 | ( 0.77, 0.94) | 0.70 | ( 0.56, 0.88) | -0.09 | (-0.14,-0.03) | |
| Yes | 559 | 345 | 61.7 | 582 | 333 | 57.2 | 0.1217 | 0.93 | ( 0.84, 1.02) | 0.83 | ( 0.65, 1.05) | -0.05 | (-0.10, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** | |
| Overall | 1188 | 416 | 35.0 | 1171 | 381 | 32.5 | 0.2028 | 0.93 ( 0.83, 1.04) | 0.89 ( 0.75, 1.06) | -0.02 (-0.06, 0.01) | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 398 | 33.5 | 1171 | 296 | 25.3 | <0.0001 | 0.75 | ( 0.66, 0.86) | 0.67 | ( 0.56, 0.80) | -0.08 | (-0.12,-0.05) | |
| Sex | | | | | | | | | | | | | | 0.7981 |
| Male | 864 | 302 | 35.0 | 837 | 219 | 26.2 | <0.0001 | 0.75 | ( 0.65, 0.87) | 0.66 | ( 0.54, 0.81) | -0.09 | (-0.13,-0.04) | |
| Female | 324 | 96 | 29.6 | 334 | 77 | 23.1 | 0.0554 | 0.78 | ( 0.60, 1.01) | 0.71 | ( 0.50, 1.01) | -0.07 | (-0.13, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.1218 |
| <65 | 569 | 165 | 29.0 | 547 | 134 | 24.5 | 0.0897 | 0.84 | ( 0.69, 1.03) | 0.79 | ( 0.61, 1.04) | -0.05 | (-0.10, 0.01) | |
| >=65 | 619 | 233 | 37.6 | 624 | 162 | 26.0 | <0.0001 | 0.69 | ( 0.58, 0.81) | 0.58 | ( 0.46, 0.74) | -0.12 | (-0.17,-0.07) | |
| Region | | | | | | | | | | | | | | 0.2572 |
| Europe | 468 | 167 | 35.7 | 434 | 119 | 27.4 | 0.0077 | 0.77 | ( 0.63, 0.93) | 0.68 | ( 0.51, 0.90) | -0.08 | (-0.14,-0.02) | |
| North America | 259 | 92 | 35.5 | 241 | 56 | 23.2 | 0.0026 | 0.65 | ( 0.49, 0.87) | 0.55 | ( 0.37, 0.81) | -0.12 | (-0.20,-0.04) | |
| Latin America | 177 | 64 | 36.2 | 191 | 52 | 27.2 | 0.0653 | 0.75 | ( 0.56, 1.02) | 0.66 | ( 0.42, 1.03) | -0.09 | (-0.18, 0.01) | |
| Africa | 50 | 19 | 38.0 | 54 | 10 | 18.5 | 0.0269 | 0.49 | ( 0.25, 0.94) | 0.37 | ( 0.15, 0.91) | -0.19 | (-0.36,-0.03) | |
| Asia | 234 | 56 | 23.9 | 251 | 59 | 23.5 | 0.9123 | 0.98 | ( 0.71, 1.35) | 0.98 | ( 0.64, 1.48) | 0.00 | (-0.08, 0.07) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3255 |
| <30 | 554 | 170 | 30.7 | 566 | 122 | 21.6 | 0.0005 | 0.70 | ( 0.57, 0.86) | 0.62 | ( 0.47, 0.81) | -0.09 | (-0.14,-0.04) | |
| >=30 | 634 | 228 | 36.0 | 605 | 174 | 28.8 | 0.0068 | 0.80 | ( 0.68, 0.94) | 0.72 | ( 0.57, 0.91) | -0.07 | (-0.12,-0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1741 |
| <130 | 379 | 140 | 36.9 | 382 | 94 | 24.6 | 0.0002 | 0.67 | ( 0.53, 0.83) | 0.56 | ( 0.41, 0.76) | -0.12 | (-0.19,-0.06) | |
| >=130 | 809 | 258 | 31.9 | 789 | 202 | 25.6 | 0.0055 | 0.80 | ( 0.69, 0.94) | 0.73 | ( 0.59, 0.91) | -0.06 | (-0.11,-0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3573 |
| <75 | 500 | 181 | 36.2 | 500 | 130 | 26.0 | 0.0005 | 0.72 | ( 0.60, 0.87) | 0.62 | ( 0.47, 0.81) | -0.10 | (-0.16,-0.04) | |
| 75 to <85 | 427 | 133 | 31.1 | 417 | 93 | 22.3 | 0.0037 | 0.72 | ( 0.57, 0.90) | 0.63 | ( 0.47, 0.86) | -0.09 | (-0.15,-0.03) | |
| >=85 | 261 | 84 | 32.2 | 254 | 73 | 28.7 | 0.3960 | 0.89 | ( 0.69, 1.16) | 0.85 | ( 0.58, 1.24) | -0.03 | (-0.11, 0.04) | |
| History of heart failure | | | | | | | | | | | | | | 0.5301 |
| No | 1048 | 322 | 30.7 | 1031 | 243 | 23.6 | 0.0002 | 0.77 | ( 0.67, 0.88) | 0.70 | ( 0.57, 0.84) | -0.07 | (-0.11,-0.03) | |
| Yes | 140 | 76 | 54.3 | 140 | 53 | 37.9 | 0.0058 | 0.70 | ( 0.54, 0.91) | 0.51 | ( 0.32, 0.83) | -0.16 | (-0.28,-0.05) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8605 |
| <45 | 179 | 71 | 39.7 | 178 | 52 | 29.2 | 0.0377 | 0.74 | ( 0.55, 0.99) | 0.63 | ( 0.40, 0.98) | -0.10 | (-0.20,-0.01) | |
| >=45 | 1009 | 327 | 32.4 | 993 | 244 | 24.6 | 0.0001 | 0.76 | ( 0.66, 0.87) | 0.68 | ( 0.56, 0.83) | -0.08 | (-0.12,-0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2356 |
| Normal (<30) | 250 | 89 | 35.6 | 257 | 71 | 27.6 | 0.0534 | 0.78 | ( 0.60, 1.01) | 0.69 | ( 0.47, 1.01) | -0.08 | (-0.16, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 225 | 33.3 | 645 | 148 | 22.9 | <0.0001 | 0.69 | ( 0.58, 0.82) | 0.60 | ( 0.47, 0.76) | -0.10 | (-0.15,-0.06) | |
| Macroalbuminuria (>300) | 260 | 84 | 32.3 | 261 | 76 | 29.1 | 0.4301 | 0.90 | ( 0.70, 1.17) | 0.86 | ( 0.59, 1.25) | -0.03 | (-0.11, 0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0520 |
| Low, moderate or high | 1018 | 341 | 33.5 | 1001 | 240 | 24.0 | <0.0001 | 0.72 | ( 0.62, 0.82) | 0.63 | ( 0.52, 0.76) | -0.10 | (-0.13,-0.06) | |
| Very high | 167 | 57 | 34.1 | 162 | 55 | 34.0 | 0.9724 | 0.99 | ( 0.74, 1.34) | 0.99 | ( 0.63, 1.57) | 0.00 | (-0.10, 0.10) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1382 |
| No | 205 | 68 | 33.2 | 211 | 42 | 19.9 | 0.0022 | 0.60 | ( 0.43, 0.84) | 0.50 | ( 0.32, 0.78) | -0.13 | (-0.22,-0.05) | |
| Yes | 983 | 330 | 33.6 | 960 | 254 | 26.5 | 0.0006 | 0.79 | ( 0.69, 0.90) | 0.71 | ( 0.59, 0.87) | -0.07 | (-0.11,-0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8922 |
| No | 422 | 117 | 27.7 | 408 | 84 | 20.6 | 0.0164 | 0.74 | ( 0.58, 0.95) | 0.68 | ( 0.49, 0.93) | -0.07 | (-0.13,-0.01) | |
| Yes | 766 | 281 | 36.7 | 763 | 212 | 27.8 | 0.0002 | 0.76 | ( 0.65, 0.88) | 0.66 | ( 0.54, 0.82) | -0.09 | (-0.14,-0.04) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5298 |
| No | 629 | 177 | 28.1 | 589 | 118 | 20.0 | 0.0010 | 0.71 | ( 0.58, 0.87) | 0.64 | ( 0.49, 0.83) | -0.08 | (-0.13,-0.03) | |
| Yes | 559 | 221 | 39.5 | 582 | 178 | 30.6 | 0.0015 | 0.77 | ( 0.66, 0.91) | 0.67 | ( 0.53, 0.86) | -0.09 | (-0.14,-0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 388 | 32.7 | 1171 | 352 | 30.1 | 0.1736 | 0.92 ( 0.82, 1.04) | 0.89 ( 0.74, 1.05) | -0.03 | (-0.06, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 386 | 32.5 | 1171 | 360 | 30.7 | 0.3611 | 0.95 ( 0.84, 1.07) | 0.92 ( 0.78, 1.10) | -0.02 | (-0.06, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 353 | 29.7 | 1171 | 296 | 25.3 | 0.0158 | 0.85 | ( 0.75, 0.97) | 0.80 | ( 0.67, 0.96) | -0.04 | (-0.08,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.1032 |
| Male | 864 | 259 | 30.0 | 837 | 228 | 27.2 | 0.2119 | 0.91 | ( 0.78, 1.06) | 0.87 | ( 0.71, 1.08) | -0.03 | (-0.07, 0.02) | |
| Female | 324 | 94 | 29.0 | 334 | 68 | 20.4 | 0.0100 | 0.70 | ( 0.53, 0.92) | 0.63 | ( 0.44, 0.90) | -0.09 | (-0.15,-0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.4460 |
| <65 | 569 | 161 | 28.3 | 547 | 124 | 22.7 | 0.0312 | 0.80 | ( 0.65, 0.98) | 0.74 | ( 0.57, 0.97) | -0.06 | (-0.11,-0.01) | |
| >=65 | 619 | 192 | 31.0 | 624 | 172 | 27.6 | 0.1809 | 0.89 | ( 0.75, 1.06) | 0.85 | ( 0.66, 1.08) | -0.03 | (-0.09, 0.02) | |
| Region | | | | | | | | | | | | | | 0.2939 |
| Europe | 468 | 106 | 22.6 | 434 | 99 | 22.8 | 0.9539 | 1.01 | ( 0.79, 1.28) | 1.01 | ( 0.74, 1.38) | 0.00 | (-0.05, 0.06) | |
| North America | 259 | 84 | 32.4 | 241 | 69 | 28.6 | 0.3567 | 0.88 | ( 0.68, 1.15) | 0.84 | ( 0.57, 1.22) | -0.04 | (-0.12, 0.04) | |
| Latin America | 177 | 65 | 36.7 | 191 | 52 | 27.2 | 0.0506 | 0.74 | ( 0.55,>1.00) | 0.64 | ( 0.41, 1.00) | -0.09 | (-0.19, 0.00) | |
| Africa | 50 | 19 | 38.0 | 54 | 18 | 33.3 | 0.6194 | 0.88 | ( 0.52, 1.47) | 0.82 | ( 0.37, 1.82) | -0.05 | (-0.23, 0.14) | |
| Asia | 234 | 79 | 33.8 | 251 | 58 | 23.1 | 0.0092 | 0.68 | ( 0.51, 0.91) | 0.59 | ( 0.40, 0.88) | -0.11 | (-0.19,-0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3637 |
| <30 | 554 | 161 | 29.1 | 566 | 131 | 23.1 | 0.0241 | 0.80 | ( 0.65, 0.97) | 0.74 | ( 0.56, 0.96) | -0.06 | (-0.11,-0.01) | |
| >=30 | 634 | 192 | 30.3 | 605 | 165 | 27.3 | 0.2421 | 0.90 | ( 0.76, 1.07) | 0.86 | ( 0.67, 1.10) | -0.03 | (-0.08, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3476 |
| <130 | 379 | 120 | 31.7 | 382 | 94 | 24.6 | 0.0304 | 0.78 | ( 0.62, 0.98) | 0.70 | ( 0.51, 0.97) | -0.07 | (-0.13,-0.01) | |
| >=130 | 809 | 233 | 28.8 | 789 | 202 | 25.6 | 0.1509 | 0.89 | ( 0.76, 1.04) | 0.85 | ( 0.68, 1.06) | -0.03 | (-0.08, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6835 |
| <75 | 500 | 152 | 30.4 | 500 | 128 | 25.6 | 0.0910 | 0.84 | ( 0.69, 1.03) | 0.79 | ( 0.60, 1.04) | -0.05 | (-0.10, 0.01) | |
| 75 to <85 | 427 | 127 | 29.7 | 417 | 100 | 24.0 | 0.0591 | 0.81 | ( 0.64, 1.01) | 0.75 | ( 0.55, 1.01) | -0.06 | (-0.12, 0.00) | |
| >=85 | 261 | 74 | 28.4 | 254 | 68 | 26.8 | 0.6882 | 0.94 | ( 0.71, 1.25) | 0.92 | ( 0.63, 1.36) | -0.02 | (-0.09, 0.06) | |
| History of heart failure | | | | | | | | | | | | | | 0.5372 |
| No | 1048 | 305 | 29.1 | 1031 | 251 | 24.3 | 0.0143 | 0.84 | ( 0.72, 0.97) | 0.78 | ( 0.65, 0.95) | -0.05 | (-0.09,-0.01) | |
| Yes | 140 | 48 | 34.3 | 140 | 45 | 32.1 | 0.7035 | 0.94 | ( 0.67, 1.31) | 0.91 | ( 0.55, 1.49) | -0.02 | (-0.13, 0.09) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1087 |
| <45 | 179 | 76 | 42.5 | 178 | 52 | 29.2 | 0.0091 | 0.69 | ( 0.52, 0.92) | 0.56 | ( 0.36, 0.87) | -0.13 | (-0.23,-0.03) | |
| >=45 | 1009 | 277 | 27.5 | 993 | 244 | 24.6 | 0.1419 | 0.90 | ( 0.77, 1.04) | 0.86 | ( 0.70, 1.05) | -0.03 | (-0.07, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.0848 |
| Normal (<30) | 250 | 84 | 33.6 | 257 | 56 | 21.8 | 0.0029 | 0.65 | ( 0.49, 0.87) | 0.55 | ( 0.37, 0.82) | -0.12 | (-0.20,-0.04) | |
| Microalbuminuria (30 to <=300) | 675 | 175 | 25.9 | 645 | 160 | 24.8 | 0.6403 | 0.96 | ( 0.80, 1.15) | 0.94 | ( 0.74, 1.21) | -0.01 | (-0.06, 0.04) | |
| Macroalbuminuria (>300) | 260 | 93 | 35.8 | 261 | 78 | 29.9 | 0.1527 | 0.84 | ( 0.65, 1.07) | 0.77 | ( 0.53, 1.10) | -0.06 | (-0.14, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1610 |
| Low, moderate or high | 1018 | 274 | 26.9 | 1001 | 240 | 24.0 | 0.1295 | 0.89 | ( 0.77, 1.03) | 0.86 | ( 0.70, 1.05) | -0.03 | (-0.07, 0.01) | |
| Very high | 167 | 78 | 46.7 | 162 | 54 | 33.3 | 0.0134 | 0.71 | ( 0.54, 0.94) | 0.57 | ( 0.37, 0.89) | -0.13 | (-0.24,-0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4599 |
| No | 205 | 66 | 32.2 | 211 | 52 | 24.6 | 0.0876 | 0.77 | ( 0.56, 1.04) | 0.69 | ( 0.45, 1.06) | -0.08 | (-0.16, 0.01) | |
| Yes | 983 | 287 | 29.2 | 960 | 244 | 25.4 | 0.0616 | 0.87 | ( 0.75, 1.01) | 0.83 | ( 0.68, 1.01) | -0.04 | (-0.08, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7942 |
| No | 422 | 127 | 30.1 | 408 | 102 | 25.0 | 0.1007 | 0.83 | ( 0.67, 1.04) | 0.77 | ( 0.57, 1.05) | -0.05 | (-0.11, 0.01) | |
| Yes | 766 | 226 | 29.5 | 763 | 194 | 25.4 | 0.0741 | 0.86 | ( 0.73, 1.01) | 0.81 | ( 0.65, 1.02) | -0.04 | (-0.09, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9523 |
| No | 629 | 166 | 26.4 | 589 | 132 | 22.4 | 0.1064 | 0.85 | ( 0.70, 1.04) | 0.81 | ( 0.62, 1.05) | -0.04 | (-0.09, 0.01) | |
| Yes | 559 | 187 | 33.5 | 582 | 164 | 28.2 | 0.0537 | 0.84 | ( 0.71,>1.00) | 0.78 | ( 0.61, 1.00) | -0.05 | (-0.11, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 347 | 29.2 | 1171 | 291 | 24.9 | 0.0172 | 0.85 | ( 0.74, 0.97) | 0.80 | ( 0.67, 0.96) | -0.04 | (-0.08,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.7475 |
| Male | 864 | 256 | 29.6 | 837 | 214 | 25.6 | 0.0611 | 0.86 | ( 0.74, 1.01) | 0.82 | ( 0.66, 1.01) | -0.04 | (-0.08, 0.00) | |
| Female | 324 | 91 | 28.1 | 334 | 77 | 23.1 | 0.1388 | 0.82 | ( 0.63, 1.07) | 0.77 | ( 0.54, 1.09) | -0.05 | (-0.12, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.1870 |
| <65 | 569 | 189 | 33.2 | 547 | 142 | 26.0 | 0.0080 | 0.78 | ( 0.65, 0.94) | 0.70 | ( 0.54, 0.91) | -0.07 | (-0.13,-0.02) | |
| >=65 | 619 | 158 | 25.5 | 624 | 149 | 23.9 | 0.5008 | 0.94 | ( 0.77, 1.14) | 0.92 | ( 0.71, 1.18) | -0.02 | (-0.06, 0.03) | |
| Region | | | | | | | | | | | | | | 0.9955 |
| Europe | 468 | 130 | 27.8 | 434 | 100 | 23.0 | 0.1030 | 0.83 | ( 0.66, 1.04) | 0.78 | ( 0.58, 1.05) | -0.05 | (-0.10, 0.01) | |
| North America | 259 | 79 | 30.5 | 241 | 64 | 26.6 | 0.3292 | 0.87 | ( 0.66, 1.15) | 0.82 | ( 0.56, 1.22) | -0.04 | (-0.12, 0.04) | |
| Latin America | 177 | 40 | 22.6 | 191 | 36 | 18.8 | 0.3745 | 0.83 | ( 0.56, 1.25) | 0.80 | ( 0.48, 1.32) | -0.04 | (-0.12, 0.05) | |
| Africa | 50 | 13 | 26.0 | 54 | 11 | 20.4 | 0.4960 | 0.78 | ( 0.39, 1.59) | 0.73 | ( 0.29, 1.82) | -0.06 | (-0.22, 0.11) | |
| Asia | 234 | 85 | 36.3 | 251 | 80 | 31.9 | 0.3011 | 0.88 | ( 0.68, 1.12) | 0.82 | ( 0.56, 1.19) | -0.04 | (-0.13, 0.04) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9846 |
| <30 | 554 | 162 | 29.2 | 566 | 141 | 24.9 | 0.1029 | 0.85 | ( 0.70, 1.03) | 0.80 | ( 0.62, 1.05) | -0.04 | (-0.10, 0.01) | |
| >=30 | 634 | 185 | 29.2 | 605 | 150 | 24.8 | 0.0823 | 0.85 | ( 0.71, 1.02) | 0.80 | ( 0.62, 1.03) | -0.04 | (-0.09, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8790 |
| <130 | 379 | 115 | 30.3 | 382 | 100 | 26.2 | 0.2020 | 0.86 | ( 0.69, 1.08) | 0.81 | ( 0.59, 1.12) | -0.04 | (-0.11, 0.02) | |
| >=130 | 809 | 232 | 28.7 | 789 | 191 | 24.2 | 0.0429 | 0.84 | ( 0.72,<1.00) | 0.79 | ( 0.64, 0.99) | -0.04 | (-0.09, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6734 |
| <75 | 500 | 150 | 30.0 | 500 | 121 | 24.2 | 0.0391 | 0.81 | ( 0.66, 0.99) | 0.74 | ( 0.56, 0.99) | -0.06 | (-0.11, 0.00) | |
| 75 to <85 | 427 | 123 | 28.8 | 417 | 102 | 24.5 | 0.1535 | 0.85 | ( 0.68, 1.06) | 0.80 | ( 0.59, 1.09) | -0.04 | (-0.10, 0.02) | |
| >=85 | 261 | 74 | 28.4 | 254 | 68 | 26.8 | 0.6882 | 0.94 | ( 0.71, 1.25) | 0.92 | ( 0.63, 1.36) | -0.02 | (-0.09, 0.06) | |
| History of heart failure | | | | | | | | | | | | | | 0.4402 |
| No | 1048 | 295 | 28.1 | 1031 | 252 | 24.4 | 0.0550 | 0.87 | ( 0.75,>1.00) | 0.83 | ( 0.68, 1.00) | -0.04 | (-0.07, 0.00) | |
| Yes | 140 | 52 | 37.1 | 140 | 39 | 27.9 | 0.0972 | 0.75 | ( 0.53, 1.06) | 0.65 | ( 0.39, 1.08) | -0.09 | (-0.20, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6252 |
| <45 | 179 | 67 | 37.4 | 178 | 53 | 29.8 | 0.1258 | 0.80 | ( 0.59, 1.07) | 0.71 | ( 0.46, 1.10) | -0.08 | (-0.17, 0.02) | |
| >=45 | 1009 | 280 | 27.8 | 993 | 238 | 24.0 | 0.0533 | 0.86 | ( 0.74,>1.00) | 0.82 | ( 0.67, 1.00) | -0.04 | (-0.08, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1854 |
| Normal (<30) | 250 | 73 | 29.2 | 257 | 57 | 22.2 | 0.0703 | 0.76 | ( 0.56, 1.02) | 0.69 | ( 0.46, 1.03) | -0.07 | (-0.15, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 180 | 26.7 | 645 | 164 | 25.4 | 0.6078 | 0.95 | ( 0.79, 1.14) | 0.94 | ( 0.73, 1.20) | -0.01 | (-0.06, 0.03) | |
| Macroalbuminuria (>300) | 260 | 94 | 36.2 | 261 | 69 | 26.4 | 0.0168 | 0.73 | ( 0.56, 0.95) | 0.63 | ( 0.44, 0.92) | -0.10 | (-0.18,-0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2826 |
| Low, moderate or high | 1018 | 277 | 27.2 | 1001 | 240 | 24.0 | 0.0960 | 0.88 | ( 0.76, 1.02) | 0.84 | ( 0.69, 1.03) | -0.03 | (-0.07, 0.01) | |
| Very high | 167 | 70 | 41.9 | 162 | 50 | 30.9 | 0.0373 | 0.74 | ( 0.55, 0.99) | 0.62 | ( 0.39, 0.97) | -0.11 | (-0.21,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4596 |
| No | 205 | 66 | 32.2 | 211 | 52 | 24.6 | 0.0876 | 0.77 | ( 0.56, 1.04) | 0.69 | ( 0.45, 1.06) | -0.08 | (-0.16, 0.01) | |
| Yes | 983 | 281 | 28.6 | 960 | 239 | 24.9 | 0.0662 | 0.87 | ( 0.75, 1.01) | 0.83 | ( 0.68, 1.01) | -0.04 | (-0.08, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9300 |
| No | 422 | 123 | 29.1 | 408 | 102 | 25.0 | 0.1791 | 0.86 | ( 0.69, 1.07) | 0.81 | ( 0.60, 1.10) | -0.04 | (-0.10, 0.02) | |
| Yes | 766 | 224 | 29.2 | 763 | 189 | 24.8 | 0.0489 | 0.85 | ( 0.72,<1.00) | 0.80 | ( 0.64, 1.00) | -0.04 | (-0.09, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3550 |
| No | 629 | 170 | 27.0 | 589 | 144 | 24.4 | 0.3039 | 0.90 | ( 0.75, 1.10) | 0.87 | ( 0.68, 1.13) | -0.03 | (-0.07, 0.02) | |
| Yes | 559 | 177 | 31.7 | 582 | 147 | 25.3 | 0.0164 | 0.80 | ( 0.66, 0.96) | 0.73 | ( 0.56, 0.94) | -0.06 | (-0.12,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 333 | 28.0 | 1171 | 260 | 22.2 | 0.0011 | 0.79 | ( 0.69, 0.91) | 0.73 | ( 0.61, 0.88) | -0.06 | (-0.09,-0.02) | |
| Sex | | | | | | | | | | | | | | 0.0776 |
| Male | 864 | 239 | 27.7 | 837 | 168 | 20.1 | 0.0002 | 0.73 | ( 0.61, 0.86) | 0.66 | ( 0.52, 0.82) | -0.08 | (-0.12,-0.04) | |
| Female | 324 | 94 | 29.0 | 334 | 92 | 27.5 | 0.6760 | 0.95 | ( 0.74, 1.21) | 0.93 | ( 0.66, 1.31) | -0.01 | (-0.08, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.9336 |
| <65 | 569 | 138 | 24.3 | 547 | 104 | 19.0 | 0.0337 | 0.78 | ( 0.63, 0.98) | 0.73 | ( 0.55, 0.98) | -0.05 | (-0.10, 0.00) | |
| >=65 | 619 | 195 | 31.5 | 624 | 156 | 25.0 | 0.0109 | 0.79 | ( 0.66, 0.95) | 0.72 | ( 0.57, 0.93) | -0.07 | (-0.11,-0.02) | |
| Region | | | | | | | | | | | | | | 0.5349 |
| Europe | 468 | 113 | 24.1 | 434 | 74 | 17.1 | 0.0086 | 0.71 | ( 0.54, 0.92) | 0.65 | ( 0.47, 0.90) | -0.07 | (-0.12,-0.02) | |
| North America | 259 | 94 | 36.3 | 241 | 71 | 29.5 | 0.1045 | 0.81 | ( 0.63, 1.05) | 0.73 | ( 0.50, 1.07) | -0.07 | (-0.15, 0.01) | |
| Latin America | 177 | 41 | 23.2 | 191 | 30 | 15.7 | 0.0701 | 0.68 | ( 0.44, 1.04) | 0.62 | ( 0.37, 1.04) | -0.07 | (-0.16, 0.01) | |
| Africa | 50 | 14 | 28.0 | 54 | 12 | 22.2 | 0.4966 | 0.79 | ( 0.41, 1.55) | 0.73 | ( 0.30, 1.79) | -0.06 | (-0.22, 0.11) | |
| Asia | 234 | 71 | 30.3 | 251 | 73 | 29.1 | 0.7619 | 0.96 | ( 0.73, 1.26) | 0.94 | ( 0.64, 1.39) | -0.01 | (-0.09, 0.07) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2556 |
| <30 | 554 | 146 | 26.4 | 566 | 129 | 22.8 | 0.1661 | 0.86 | ( 0.70, 1.06) | 0.82 | ( 0.63, 1.08) | -0.04 | (-0.09, 0.01) | |
| >=30 | 634 | 187 | 29.5 | 605 | 131 | 21.7 | 0.0016 | 0.73 | ( 0.60, 0.89) | 0.66 | ( 0.51, 0.86) | -0.08 | (-0.13,-0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8390 |
| <130 | 379 | 108 | 28.5 | 382 | 88 | 23.0 | 0.0851 | 0.81 | ( 0.63, 1.03) | 0.75 | ( 0.54, 1.04) | -0.05 | (-0.12, 0.01) | |
| >=130 | 809 | 225 | 27.8 | 789 | 172 | 21.8 | 0.0054 | 0.78 | ( 0.66, 0.93) | 0.72 | ( 0.58, 0.91) | -0.06 | (-0.10,-0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8859 |
| <75 | 500 | 159 | 31.8 | 500 | 124 | 24.8 | 0.0140 | 0.78 | ( 0.64, 0.95) | 0.71 | ( 0.54, 0.93) | -0.07 | (-0.13,-0.01) | |
| 75 to <85 | 427 | 115 | 26.9 | 417 | 87 | 20.9 | 0.0388 | 0.77 | ( 0.61, 0.99) | 0.72 | ( 0.52, 0.98) | -0.06 | (-0.12, 0.00) | |
| >=85 | 261 | 59 | 22.6 | 254 | 49 | 19.3 | 0.3557 | 0.85 | ( 0.61, 1.20) | 0.82 | ( 0.53, 1.25) | -0.03 | (-0.10, 0.04) | |
| History of heart failure | | | | | | | | | | | | | | 0.6473 |
| No | 1048 | 289 | 27.6 | 1031 | 228 | 22.1 | 0.0040 | 0.80 | ( 0.69, 0.93) | 0.75 | ( 0.61, 0.91) | -0.05 | (-0.09,-0.02) | |
| Yes | 140 | 44 | 31.4 | 140 | 32 | 22.9 | 0.1068 | 0.73 | ( 0.49, 1.07) | 0.65 | ( 0.38, 1.10) | -0.09 | (-0.19, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6153 |
| <45 | 179 | 59 | 33.0 | 178 | 50 | 28.1 | 0.3177 | 0.85 | ( 0.62, 1.17) | 0.79 | ( 0.51, 1.25) | -0.05 | (-0.14, 0.05) | |
| >=45 | 1009 | 274 | 27.2 | 993 | 210 | 21.1 | 0.0017 | 0.78 | ( 0.67, 0.91) | 0.72 | ( 0.59, 0.88) | -0.06 | (-0.10,-0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1278 |
| Normal (<30) | 250 | 64 | 25.6 | 257 | 64 | 24.9 | 0.8566 | 0.97 | ( 0.72, 1.31) | 0.96 | ( 0.65, 1.44) | -0.01 | (-0.08, 0.07) | |
| Microalbuminuria (30 to <=300) | 675 | 188 | 27.9 | 645 | 124 | 19.2 | 0.0002 | 0.69 | ( 0.57, 0.84) | 0.62 | ( 0.48, 0.80) | -0.09 | (-0.13,-0.04) | |
| Macroalbuminuria (>300) | 260 | 80 | 30.8 | 261 | 70 | 26.8 | 0.3195 | 0.87 | ( 0.66, 1.14) | 0.82 | ( 0.56, 1.21) | -0.04 | (-0.12, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5177 |
| Low, moderate or high | 1018 | 265 | 26.0 | 1001 | 211 | 21.1 | 0.0088 | 0.81 | ( 0.69, 0.95) | 0.76 | ( 0.62, 0.93) | -0.05 | (-0.09,-0.01) | |
| Very high | 167 | 67 | 40.1 | 162 | 47 | 29.0 | 0.0343 | 0.72 | ( 0.53, 0.98) | 0.61 | ( 0.39, 0.97) | -0.11 | (-0.21,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7938 |
| No | 205 | 59 | 28.8 | 211 | 50 | 23.7 | 0.2384 | 0.82 | ( 0.60, 1.14) | 0.77 | ( 0.50, 1.19) | -0.05 | (-0.14, 0.03) | |
| Yes | 983 | 274 | 27.9 | 960 | 210 | 21.9 | 0.0022 | 0.78 | ( 0.67, 0.92) | 0.72 | ( 0.59, 0.89) | -0.06 | (-0.10,-0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5712 |
| No | 422 | 111 | 26.3 | 408 | 80 | 19.6 | 0.0220 | 0.75 | ( 0.58, 0.96) | 0.68 | ( 0.49, 0.95) | -0.07 | (-0.12,-0.01) | |
| Yes | 766 | 222 | 29.0 | 763 | 180 | 23.6 | 0.0167 | 0.81 | ( 0.69, 0.96) | 0.76 | ( 0.60, 0.95) | -0.05 | (-0.10,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.0600 |
| No | 629 | 149 | 23.7 | 589 | 127 | 21.6 | 0.3757 | 0.91 | ( 0.74, 1.12) | 0.89 | ( 0.68, 1.16) | -0.02 | (-0.07, 0.03) | |
| Yes | 559 | 184 | 32.9 | 582 | 133 | 22.9 | 0.0001 | 0.69 | ( 0.57, 0.84) | 0.60 | ( 0.46, 0.78) | -0.10 | (-0.15,-0.05) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 284 | 23.9 | 1171 | 243 | 20.8 | 0.0659 | 0.87 ( 0.75, 1.01) | 0.83 ( 0.69, 1.01) | -0.03 | (-0.07, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 275 | 23.1 | 1171 | 203 | 17.3 | 0.0004 | 0.75 | ( 0.64, 0.88) | 0.70 | ( 0.57, 0.85) | -0.06 | (-0.09,-0.03) | |
| Sex | | | | | | | | | | | | | | 0.9540 |
| Male | 864 | 194 | 22.5 | 837 | 141 | 16.8 | 0.0036 | 0.75 | ( 0.62, 0.91) | 0.70 | ( 0.55, 0.89) | -0.06 | (-0.09,-0.02) | |
| Female | 324 | 81 | 25.0 | 334 | 62 | 18.6 | 0.0453 | 0.74 | ( 0.55,<1.00) | 0.68 | ( 0.47, 0.99) | -0.06 | (-0.13, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.1622 |
| <65 | 569 | 108 | 19.0 | 547 | 89 | 16.3 | 0.2352 | 0.86 | ( 0.66, 1.11) | 0.83 | ( 0.61, 1.13) | -0.03 | (-0.07, 0.02) | |
| >=65 | 619 | 167 | 27.0 | 624 | 114 | 18.3 | 0.0002 | 0.68 | ( 0.55, 0.84) | 0.61 | ( 0.46, 0.79) | -0.09 | (-0.13,-0.04) | |
| Region | | | | | | | | | | | | | | 0.1440 |
| Europe | 468 | 87 | 18.6 | 434 | 75 | 17.3 | 0.6089 | 0.93 | ( 0.70, 1.23) | 0.91 | ( 0.65, 1.29) | -0.01 | (-0.06, 0.04) | |
| North America | 259 | 91 | 35.1 | 241 | 50 | 20.7 | 0.0004 | 0.59 | ( 0.44, 0.79) | 0.48 | ( 0.32, 0.72) | -0.14 | (-0.22,-0.07) | |
| Latin America | 177 | 32 | 18.1 | 191 | 27 | 14.1 | 0.3030 | 0.78 | ( 0.49, 1.25) | 0.75 | ( 0.43, 1.30) | -0.04 | (-0.11, 0.04) | |
| Africa | 50 | 9 | 18.0 | 54 | 3 | 5.6 | 0.0472 | 0.31 | ( 0.09, 1.08) | 0.27 | ( 0.07, 1.05) | -0.12 | (-0.25, 0.00) | |
| Asia | 234 | 56 | 23.9 | 251 | 48 | 19.1 | 0.1973 | 0.80 | ( 0.57, 1.12) | 0.75 | ( 0.49, 1.16) | -0.05 | (-0.12, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0430 |
| <30 | 554 | 124 | 22.4 | 566 | 78 | 13.8 | 0.0002 | 0.62 | ( 0.48, 0.80) | 0.55 | ( 0.41, 0.76) | -0.09 | (-0.13,-0.04) | |
| >=30 | 634 | 151 | 23.8 | 605 | 125 | 20.7 | 0.1820 | 0.87 | ( 0.70, 1.07) | 0.83 | ( 0.64, 1.09) | -0.03 | (-0.08, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0247 |
| <130 | 379 | 105 | 27.7 | 382 | 61 | 16.0 | <0.0001 | 0.58 | ( 0.43, 0.76) | 0.50 | ( 0.35, 0.71) | -0.12 | (-0.18,-0.06) | |
| >=130 | 809 | 170 | 21.0 | 789 | 142 | 18.0 | 0.1283 | 0.86 | ( 0.70, 1.05) | 0.82 | ( 0.64, 1.06) | -0.03 | (-0.07, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1873 |
| <75 | 500 | 141 | 28.2 | 500 | 97 | 19.4 | 0.0011 | 0.69 | ( 0.55, 0.86) | 0.61 | ( 0.46, 0.82) | -0.09 | (-0.14,-0.04) | |
| 75 to <85 | 427 | 90 | 21.1 | 417 | 62 | 14.9 | 0.0189 | 0.71 | ( 0.53, 0.95) | 0.65 | ( 0.46, 0.93) | -0.06 | (-0.11,-0.01) | |
| >=85 | 261 | 44 | 16.9 | 254 | 44 | 17.3 | 0.8886 | 1.03 | ( 0.70, 1.50) | 1.03 | ( 0.65, 1.64) | 0.00 | (-0.06, 0.07) | |
| History of heart failure | | | | | | | | | | | | | | 0.2244 |
| No | 1048 | 225 | 21.5 | 1031 | 173 | 16.8 | 0.0066 | 0.78 | ( 0.65, 0.93) | 0.74 | ( 0.59, 0.92) | -0.05 | (-0.08,-0.01) | |
| Yes | 140 | 50 | 35.7 | 140 | 30 | 21.4 | 0.0082 | 0.60 | ( 0.41, 0.88) | 0.49 | ( 0.29, 0.84) | -0.14 | (-0.25,-0.04) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6623 |
| <45 | 179 | 46 | 25.7 | 178 | 37 | 20.8 | 0.2720 | 0.81 | ( 0.55, 1.18) | 0.76 | ( 0.46, 1.24) | -0.05 | (-0.14, 0.04) | |
| >=45 | 1009 | 229 | 22.7 | 993 | 166 | 16.7 | 0.0008 | 0.74 | ( 0.62, 0.88) | 0.68 | ( 0.55, 0.85) | -0.06 | (-0.09,-0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6206 |
| Normal (<30) | 250 | 63 | 25.2 | 257 | 44 | 17.1 | 0.0258 | 0.68 | ( 0.48, 0.96) | 0.61 | ( 0.40, 0.94) | -0.08 | (-0.15,-0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 144 | 21.3 | 645 | 101 | 15.7 | 0.0080 | 0.73 | ( 0.58, 0.92) | 0.68 | ( 0.52, 0.91) | -0.06 | (-0.10,-0.02) | |
| Macroalbuminuria (>300) | 260 | 67 | 25.8 | 261 | 57 | 21.8 | 0.2922 | 0.85 | ( 0.62, 1.15) | 0.80 | ( 0.54, 1.21) | -0.04 | (-0.11, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7606 |
| Low, moderate or high | 1018 | 222 | 21.8 | 1001 | 166 | 16.6 | 0.0029 | 0.76 | ( 0.63, 0.91) | 0.71 | ( 0.57, 0.89) | -0.05 | (-0.09,-0.02) | |
| Very high | 167 | 52 | 31.1 | 162 | 36 | 22.2 | 0.0678 | 0.71 | ( 0.49, 1.03) | 0.63 | ( 0.39, 1.04) | -0.09 | (-0.18, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7879 |
| No | 205 | 49 | 23.9 | 211 | 36 | 17.1 | 0.0836 | 0.71 | ( 0.49, 1.05) | 0.65 | ( 0.40, 1.06) | -0.07 | (-0.15, 0.01) | |
| Yes | 983 | 226 | 23.0 | 960 | 167 | 17.4 | 0.0021 | 0.76 | ( 0.63, 0.91) | 0.71 | ( 0.56, 0.88) | -0.06 | (-0.09,-0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6900 |
| No | 422 | 91 | 21.6 | 408 | 69 | 16.9 | 0.0894 | 0.78 | ( 0.59, 1.04) | 0.74 | ( 0.52, 1.05) | -0.05 | (-0.10, 0.01) | |
| Yes | 766 | 184 | 24.0 | 763 | 134 | 17.6 | 0.0019 | 0.73 | ( 0.60, 0.89) | 0.67 | ( 0.53, 0.86) | -0.06 | (-0.11,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3991 |
| No | 629 | 125 | 19.9 | 589 | 94 | 16.0 | 0.0755 | 0.80 | ( 0.63, 1.02) | 0.77 | ( 0.57, 1.03) | -0.04 | (-0.08, 0.00) | |
| Yes | 559 | 150 | 26.8 | 582 | 109 | 18.7 | 0.0011 | 0.70 | ( 0.56, 0.87) | 0.63 | ( 0.47, 0.83) | -0.08 | (-0.13,-0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 235 | 19.8 | 1171 | 206 | 17.6 | 0.1727 | 0.89 ( 0.75, 1.05) | 0.87 ( 0.70, 1.07) | -0.02 | (-0.05, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 234 | 19.7 | 1171 | 192 | 16.4 | 0.0372 | 0.83 | ( 0.70, 0.99) | 0.80 | ( 0.65, 0.99) | -0.03 | (-0.06, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0174 |
| Male | 864 | 165 | 19.1 | 837 | 151 | 18.0 | 0.5754 | 0.94 | ( 0.77, 1.15) | 0.93 | ( 0.73, 1.19) | -0.01 | (-0.05, 0.03) | |
| Female | 324 | 69 | 21.3 | 334 | 41 | 12.3 | 0.0019 | 0.58 | ( 0.40, 0.82) | 0.52 | ( 0.34, 0.79) | -0.09 | (-0.15,-0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.2174 |
| <65 | 569 | 108 | 19.0 | 547 | 76 | 13.9 | 0.0221 | 0.73 | ( 0.56, 0.96) | 0.69 | ( 0.50, 0.95) | -0.05 | (-0.09,-0.01) | |
| >=65 | 619 | 126 | 20.4 | 624 | 116 | 18.6 | 0.4318 | 0.91 | ( 0.73, 1.15) | 0.89 | ( 0.67, 1.18) | -0.02 | (-0.06, 0.03) | |
| Region | | | | | | | | | | | | | | 0.6518 |
| Europe | 468 | 89 | 19.0 | 434 | 57 | 13.1 | 0.0165 | 0.69 | ( 0.51, 0.94) | 0.64 | ( 0.45, 0.92) | -0.06 | (-0.11,-0.01) | |
| North America | 259 | 62 | 23.9 | 241 | 50 | 20.7 | 0.3924 | 0.87 | ( 0.62, 1.20) | 0.83 | ( 0.55, 1.27) | -0.03 | (-0.10, 0.04) | |
| Latin America | 177 | 28 | 15.8 | 191 | 28 | 14.7 | 0.7570 | 0.93 | ( 0.57, 1.50) | 0.91 | ( 0.52, 1.61) | -0.01 | (-0.09, 0.06) | |
| Africa | 50 | 9 | 18.0 | 54 | 10 | 18.5 | 0.9455 | 1.03 | ( 0.46, 2.32) | 1.04 | ( 0.38, 2.80) | 0.01 | (-0.14, 0.15) | |
| Asia | 234 | 46 | 19.7 | 251 | 47 | 18.7 | 0.7942 | 0.95 | ( 0.66, 1.37) | 0.94 | ( 0.60, 1.48) | -0.01 | (-0.08, 0.06) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7027 |
| <30 | 554 | 106 | 19.1 | 566 | 87 | 15.4 | 0.0955 | 0.80 | ( 0.62, 1.04) | 0.77 | ( 0.56, 1.05) | -0.04 | (-0.08, 0.01) | |
| >=30 | 634 | 128 | 20.2 | 605 | 105 | 17.4 | 0.2019 | 0.86 | ( 0.68, 1.08) | 0.83 | ( 0.62, 1.11) | -0.03 | (-0.07, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7405 |
| <130 | 379 | 71 | 18.7 | 382 | 57 | 14.9 | 0.1598 | 0.80 | ( 0.58, 1.10) | 0.76 | ( 0.52, 1.11) | -0.04 | (-0.09, 0.01) | |
| >=130 | 809 | 163 | 20.1 | 789 | 135 | 17.1 | 0.1190 | 0.85 | ( 0.69, 1.04) | 0.82 | ( 0.64, 1.05) | -0.03 | (-0.07, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4321 |
| <75 | 500 | 115 | 23.0 | 500 | 87 | 17.4 | 0.0274 | 0.76 | ( 0.59, 0.97) | 0.71 | ( 0.52, 0.96) | -0.06 | (-0.11,-0.01) | |
| 75 to <85 | 427 | 77 | 18.0 | 417 | 63 | 15.1 | 0.2534 | 0.84 | ( 0.62, 1.14) | 0.81 | ( 0.56, 1.16) | -0.03 | (-0.08, 0.02) | |
| >=85 | 261 | 42 | 16.1 | 254 | 42 | 16.5 | 0.8917 | 1.03 | ( 0.69, 1.52) | 1.03 | ( 0.65, 1.65) | 0.00 | (-0.06, 0.07) | |
| History of heart failure | | | | | | | | | | | | | | 0.3174 |
| No | 1048 | 202 | 19.3 | 1031 | 171 | 16.6 | 0.1101 | 0.86 | ( 0.72, 1.03) | 0.83 | ( 0.67, 1.04) | -0.03 | (-0.06, 0.01) | |
| Yes | 140 | 32 | 22.9 | 140 | 21 | 15.0 | 0.0933 | 0.66 | ( 0.40, 1.08) | 0.60 | ( 0.32, 1.09) | -0.08 | (-0.17, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7749 |
| <45 | 179 | 47 | 26.3 | 178 | 37 | 20.8 | 0.2231 | 0.79 | ( 0.54, 1.15) | 0.74 | ( 0.45, 1.21) | -0.05 | (-0.14, 0.03) | |
| >=45 | 1009 | 187 | 18.5 | 993 | 155 | 15.6 | 0.0822 | 0.84 | ( 0.69, 1.02) | 0.81 | ( 0.64, 1.03) | -0.03 | (-0.06, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5197 |
| Normal (<30) | 250 | 46 | 18.4 | 257 | 32 | 12.5 | 0.0635 | 0.68 | ( 0.45, 1.03) | 0.63 | ( 0.39, 1.03) | -0.06 | (-0.12, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 124 | 18.4 | 645 | 106 | 16.4 | 0.3539 | 0.89 | ( 0.71, 1.13) | 0.87 | ( 0.66, 1.16) | -0.02 | (-0.06, 0.02) | |
| Macroalbuminuria (>300) | 260 | 64 | 24.6 | 261 | 54 | 20.7 | 0.2844 | 0.84 | ( 0.61, 1.16) | 0.80 | ( 0.53, 1.21) | -0.04 | (-0.11, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9181 |
| Low, moderate or high | 1018 | 188 | 18.5 | 1001 | 154 | 15.4 | 0.0648 | 0.83 | ( 0.69, 1.01) | 0.80 | ( 0.64, 1.01) | -0.03 | (-0.06, 0.00) | |
| Very high | 167 | 46 | 27.5 | 162 | 38 | 23.5 | 0.3952 | 0.85 | ( 0.59, 1.23) | 0.81 | ( 0.49, 1.33) | -0.04 | (-0.13, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6948 |
| No | 205 | 39 | 19.0 | 211 | 36 | 17.1 | 0.6026 | 0.90 | ( 0.60, 1.35) | 0.88 | ( 0.53, 1.44) | -0.02 | (-0.09, 0.05) | |
| Yes | 983 | 195 | 19.8 | 960 | 156 | 16.3 | 0.0399 | 0.82 | ( 0.68, 0.99) | 0.78 | ( 0.62, 0.99) | -0.04 | (-0.07, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4102 |
| No | 422 | 80 | 19.0 | 408 | 71 | 17.4 | 0.5615 | 0.92 | ( 0.69, 1.23) | 0.90 | ( 0.63, 1.28) | -0.02 | (-0.07, 0.04) | |
| Yes | 766 | 154 | 20.1 | 763 | 121 | 15.9 | 0.0307 | 0.79 | ( 0.64, 0.98) | 0.75 | ( 0.58, 0.97) | -0.04 | (-0.08, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6839 |
| No | 629 | 119 | 18.9 | 589 | 96 | 16.3 | 0.2307 | 0.86 | ( 0.67, 1.10) | 0.83 | ( 0.62, 1.12) | -0.03 | (-0.07, 0.02) | |
| Yes | 559 | 115 | 20.6 | 582 | 96 | 16.5 | 0.0761 | 0.80 | ( 0.63, 1.02) | 0.76 | ( 0.57, 1.03) | -0.04 | (-0.09, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 168 | 14.1 | 1171 | 158 | 13.5 | 0.6481 | 0.95 ( 0.78, 1.17) | 0.95 ( 0.75, 1.20) | -0.01 | (-0.03, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 149 | 12.5 | 1171 | 119 | 10.2 | 0.0686 | 0.81 ( 0.65, 1.02) | 0.79 ( 0.61, 1.02) | -0.02 (-0.05, 0.00) | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 137 | 11.5 | 1171 | 110 | 9.4 | 0.0899 | 0.81 ( 0.64, 1.03) | 0.80 ( 0.61, 1.04) | -0.02 (-0.05, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 108 | 9.1 | 1171 | 101 | 8.6 | 0.6906 | 0.95 ( 0.73, 1.23) | 0.94 ( 0.71, 1.25) | 0.00 | (-0.03, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Reproductive system and breast disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 84 | 7.1 | 1171 | 99 | 8.5 | 0.2091 | 1.20 ( 0.90, 1.58) | 1.21 ( 0.90, 1.64) | 0.01 (-0.01, 0.04) | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Ear and labyrinth disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 84 | 7.1 | 1171 | 57 | 4.9 | 0.0240 | 0.69 | ( 0.50, 0.95) | 0.67 | ( 0.48, 0.95) | -0.02 | (-0.04, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.7412 |
| Male | 864 | 55 | 6.4 | 837 | 35 | 4.2 | 0.0442 | 0.66 | ( 0.43, 0.99) | 0.64 | ( 0.42, 0.99) | -0.02 | (-0.04, 0.00) | |
| Female | 324 | 29 | 9.0 | 334 | 22 | 6.6 | 0.2569 | 0.74 | ( 0.43, 1.25) | 0.72 | ( 0.40, 1.28) | -0.02 | (-0.06, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.9873 |
| <65 | 569 | 29 | 5.1 | 547 | 19 | 3.5 | 0.1815 | 0.68 | ( 0.39, 1.20) | 0.67 | ( 0.37, 1.21) | -0.02 | (-0.04, 0.01) | |
| >=65 | 619 | 55 | 8.9 | 624 | 38 | 6.1 | 0.0611 | 0.69 | ( 0.46, 1.02) | 0.66 | ( 0.43, 1.02) | -0.03 | (-0.06, 0.00) | |
| Region | | | | | | | | | | | | | | 0.1787 |
| Europe | 468 | 28 | 6.0 | 434 | 8 | 1.8 | 0.0015 | 0.31 | ( 0.14, 0.67) | 0.30 | ( 0.13, 0.65) | -0.04 | (-0.07,-0.02) | |
| North America | 259 | 28 | 10.8 | 241 | 20 | 8.3 | 0.3407 | 0.77 | ( 0.44, 1.33) | 0.75 | ( 0.41, 1.36) | -0.03 | (-0.08, 0.03) | |
| Latin America | 177 | 6 | 3.4 | 191 | 6 | 3.1 | 0.8933 | 0.93 | ( 0.30, 2.82) | 0.92 | ( 0.29, 2.92) | 0.00 | (-0.04, 0.03) | |
| Africa | 50 | 3 | 6.0 | 54 | 2 | 3.7 | 0.5844 | 0.62 | ( 0.11, 3.54) | 0.60 | ( 0.10, 3.76) | -0.02 | (-0.11, 0.06) | |
| Asia | 234 | 19 | 8.1 | 251 | 21 | 8.4 | 0.9213 | 1.03 | ( 0.57, 1.87) | 1.03 | ( 0.54, 1.97) | 0.00 | (-0.05, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1262 |
| <30 | 554 | 35 | 6.3 | 566 | 32 | 5.7 | 0.6395 | 0.89 | ( 0.56, 1.42) | 0.89 | ( 0.54, 1.46) | -0.01 | (-0.03, 0.02) | |
| >=30 | 634 | 49 | 7.7 | 605 | 25 | 4.1 | 0.0076 | 0.53 | ( 0.33, 0.85) | 0.51 | ( 0.31, 0.84) | -0.04 | (-0.06,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3233 |
| <130 | 379 | 31 | 8.2 | 382 | 17 | 4.5 | 0.0344 | 0.54 | ( 0.31, 0.97) | 0.52 | ( 0.28, 0.96) | -0.04 | (-0.07, 0.00) | |
| >=130 | 809 | 53 | 6.6 | 789 | 40 | 5.1 | 0.2059 | 0.77 | ( 0.52, 1.15) | 0.76 | ( 0.50, 1.16) | -0.01 | (-0.04, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7751 |
| <75 | 500 | 45 | 9.0 | 500 | 32 | 6.4 | 0.1231 | 0.71 | ( 0.46, 1.10) | 0.69 | ( 0.43, 1.11) | -0.03 | (-0.06, 0.01) | |
| 75 to <85 | 427 | 28 | 6.6 | 417 | 16 | 3.8 | 0.0755 | 0.59 | ( 0.32, 1.07) | 0.57 | ( 0.30, 1.07) | -0.03 | (-0.06, 0.00) | |
| >=85 | 261 | 11 | 4.2 | 254 | 9 | 3.5 | 0.6934 | 0.84 | ( 0.35, 1.99) | 0.83 | ( 0.34, 2.05) | -0.01 | (-0.04, 0.03) | |
| History of heart failure | | | | | | | | | | | | | | 0.2085 |
| No | 1048 | 69 | 6.6 | 1031 | 51 | 4.9 | 0.1095 | 0.75 | ( 0.53, 1.07) | 0.74 | ( 0.51, 1.07) | -0.02 | (-0.04, 0.00) | |
| Yes | 140 | 15 | 10.7 | 140 | 6 | 4.3 | 0.0411 | 0.40 | ( 0.16,>1.00) | 0.37 | ( 0.14, 0.99) | -0.06 | (-0.13, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Ear and labyrinth disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6619 |
| <45 | 179 | 17 | 9.5 | 178 | 10 | 5.6 | 0.1657 | 0.59 | ( 0.28, 1.26) | 0.57 | ( 0.25, 1.28) | -0.04 | (-0.09, 0.02) | |
| >=45 | 1009 | 67 | 6.6 | 993 | 47 | 4.7 | 0.0656 | 0.71 | ( 0.50, 1.02) | 0.70 | ( 0.48, 1.03) | -0.02 | (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.0044 |
| Normal (<30) | 250 | 32 | 12.8 | 257 | 14 | 5.4 | 0.0040 | 0.43 | ( 0.23, 0.78) | 0.39 | ( 0.20, 0.75) | -0.07 | (-0.12,-0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 44 | 6.5 | 645 | 25 | 3.9 | 0.0311 | 0.59 | ( 0.37, 0.96) | 0.58 | ( 0.35, 0.96) | -0.03 | (-0.05, 0.00) | |
| Macroalbuminuria (>300) | 260 | 8 | 3.1 | 261 | 18 | 6.9 | 0.0453 | 2.24 | ( 0.99, 5.06) | 2.33 | ( 1.00, 5.47) | 0.04 | ( 0.00, 0.08) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2045 |
| Low, moderate or high | 1018 | 74 | 7.3 | 1001 | 46 | 4.6 | 0.0111 | 0.63 | ( 0.44, 0.90) | 0.61 | ( 0.42, 0.90) | -0.03 | (-0.05,-0.01) | |
| Very high | 167 | 10 | 6.0 | 162 | 11 | 6.8 | 0.7660 | 1.13 | ( 0.50, 2.60) | 1.14 | ( 0.47, 2.77) | 0.01 | (-0.04, 0.06) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3283 |
| No | 205 | 18 | 8.8 | 211 | 9 | 4.3 | 0.0616 | 0.49 | ( 0.22, 1.06) | 0.46 | ( 0.20, 1.06) | -0.05 | (-0.09, 0.00) | |
| Yes | 983 | 66 | 6.7 | 960 | 48 | 5.0 | 0.1080 | 0.74 | ( 0.52, 1.07) | 0.73 | ( 0.50, 1.07) | -0.02 | (-0.04, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5714 |
| No | 422 | 22 | 5.2 | 408 | 17 | 4.2 | 0.4763 | 0.80 | ( 0.43, 1.48) | 0.79 | ( 0.41, 1.51) | -0.01 | (-0.04, 0.02) | |
| Yes | 766 | 62 | 8.1 | 763 | 40 | 5.2 | 0.0255 | 0.65 | ( 0.44, 0.95) | 0.63 | ( 0.42, 0.95) | -0.03 | (-0.05, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.0633 |
| No | 629 | 32 | 5.1 | 589 | 29 | 4.9 | 0.8958 | 0.97 | ( 0.59, 1.58) | 0.97 | ( 0.58, 1.62) | 0.00 | (-0.03, 0.02) | |
| Yes | 559 | 52 | 9.3 | 582 | 28 | 4.8 | 0.0030 | 0.52 | ( 0.33, 0.81) | 0.49 | ( 0.31, 0.79) | -0.04 | (-0.07,-0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 64 | 5.4 | 1171 | 38 | 3.2 | 0.0105 | 0.60 | ( 0.41, 0.89) | 0.59 | ( 0.39, 0.89) | -0.02 | (-0.04,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.2070 |
| Male | 864 | 44 | 5.1 | 837 | 30 | 3.6 | 0.1273 | 0.70 | ( 0.45, 1.11) | 0.69 | ( 0.43, 1.11) | -0.02 | (-0.03, 0.00) | |
| Female | 324 | 20 | 6.2 | 334 | 8 | 2.4 | 0.0164 | 0.39 | ( 0.17, 0.87) | 0.37 | ( 0.16, 0.86) | -0.04 | (-0.07,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.1227 |
| <65 | 569 | 29 | 5.1 | 547 | 11 | 2.0 | 0.0056 | 0.39 | ( 0.20, 0.78) | 0.38 | ( 0.19, 0.77) | -0.03 | (-0.05,-0.01) | |
| >=65 | 619 | 35 | 5.7 | 624 | 27 | 4.3 | 0.2825 | 0.77 | ( 0.47, 1.25) | 0.75 | ( 0.45, 1.26) | -0.01 | (-0.04, 0.01) | |
| Region | | | | | | | | | | | | | | 0.6878 |
| Europe | 468 | 19 | 4.1 | 434 | 8 | 1.8 | 0.0510 | 0.45 | ( 0.20, 1.03) | 0.44 | ( 0.19, 1.02) | -0.02 | (-0.04, 0.00) | |
| North America | 259 | 11 | 4.2 | 241 | 10 | 4.1 | 0.9566 | 0.98 | ( 0.42, 2.26) | 0.98 | ( 0.41, 2.34) | 0.00 | (-0.04, 0.03) | |
| Latin America | 177 | 13 | 7.3 | 191 | 9 | 4.7 | 0.2872 | 0.64 | ( 0.28, 1.46) | 0.62 | ( 0.26, 1.50) | -0.03 | (-0.08, 0.02) | |
| Africa | 50 | 3 | 6.0 | 54 | 1 | 1.9 | 0.2717 | 0.31 | ( 0.03, 2.87) | 0.30 | ( 0.03, 2.94) | -0.04 | (-0.12, 0.03) | |
| Asia | 234 | 18 | 7.7 | 251 | 10 | 4.0 | 0.0802 | 0.52 | ( 0.24, 1.10) | 0.50 | ( 0.22, 1.10) | -0.04 | (-0.08, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8873 |
| <30 | 554 | 30 | 5.4 | 566 | 19 | 3.4 | 0.0922 | 0.62 | ( 0.35, 1.09) | 0.61 | ( 0.34, 1.09) | -0.02 | (-0.04, 0.00) | |
| >=30 | 634 | 34 | 5.4 | 605 | 19 | 3.1 | 0.0533 | 0.59 | ( 0.34, 1.02) | 0.57 | ( 0.32, 1.01) | -0.02 | (-0.04, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2446 |
| <130 | 379 | 27 | 7.1 | 382 | 12 | 3.1 | 0.0127 | 0.44 | ( 0.23, 0.86) | 0.42 | ( 0.21, 0.85) | -0.04 | (-0.07,-0.01) | |
| >=130 | 809 | 37 | 4.6 | 789 | 26 | 3.3 | 0.1893 | 0.72 | ( 0.44, 1.18) | 0.71 | ( 0.43, 1.19) | -0.01 | (-0.03, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1689 |
| <75 | 500 | 24 | 4.8 | 500 | 20 | 4.0 | 0.5374 | 0.83 | ( 0.47, 1.49) | 0.83 | ( 0.45, 1.52) | -0.01 | (-0.03, 0.02) | |
| 75 to <85 | 427 | 24 | 5.6 | 417 | 14 | 3.4 | 0.1129 | 0.60 | ( 0.31, 1.14) | 0.58 | ( 0.30, 1.14) | -0.02 | (-0.05, 0.01) | |
| >=85 | 261 | 16 | 6.1 | 254 | 4 | 1.6 | 0.0075 | 0.26 | ( 0.09, 0.76) | 0.25 | ( 0.08, 0.74) | -0.05 | (-0.08,-0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.7516 |
| No | 1048 | 57 | 5.4 | 1031 | 33 | 3.2 | 0.0122 | 0.59 | ( 0.39, 0.90) | 0.57 | ( 0.37, 0.89) | -0.02 | (-0.04, 0.00) | |
| Yes | 140 | 7 | 5.0 | 140 | 5 | 3.6 | 0.5551 | 0.71 | ( 0.23, 2.20) | 0.70 | ( 0.22, 2.27) | -0.01 | (-0.06, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9437 |
| <45 | 179 | 13 | 7.3 | 178 | 8 | 4.5 | 0.2664 | 0.62 | ( 0.26, 1.46) | 0.60 | ( 0.24, 1.49) | -0.03 | (-0.08, 0.02) | |
| >=45 | 1009 | 51 | 5.1 | 993 | 30 | 3.0 | 0.0210 | 0.60 | ( 0.38, 0.93) | 0.59 | ( 0.37, 0.93) | -0.02 | (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1584 |
| Normal (<30) | 250 | 11 | 4.4 | 257 | 9 | 3.5 | 0.6035 | 0.80 | ( 0.34, 1.89) | 0.79 | ( 0.32, 1.94) | -0.01 | (-0.04, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 40 | 5.9 | 645 | 16 | 2.5 | 0.0019 | 0.42 | ( 0.24, 0.74) | 0.40 | ( 0.22, 0.73) | -0.03 | (-0.06,-0.01) | |
| Macroalbuminuria (>300) | 260 | 13 | 5.0 | 261 | 13 | 5.0 | 0.9920 | 1.00 | ( 0.47, 2.11) | 1.00 | ( 0.45, 2.19) | 0.00 | (-0.04, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8709 |
| Low, moderate or high | 1018 | 53 | 5.2 | 1001 | 32 | 3.2 | 0.0246 | 0.61 | ( 0.40, 0.94) | 0.60 | ( 0.38, 0.94) | -0.02 | (-0.04, 0.00) | |
| Very high | 167 | 11 | 6.6 | 162 | 6 | 3.7 | 0.2376 | 0.56 | ( 0.21, 1.48) | 0.55 | ( 0.20, 1.51) | -0.03 | (-0.08, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2265 |
| No | 205 | 16 | 7.8 | 211 | 6 | 2.8 | 0.0238 | 0.36 | ( 0.15, 0.91) | 0.35 | ( 0.13, 0.90) | -0.05 | (-0.09,-0.01) | |
| Yes | 983 | 48 | 4.9 | 960 | 32 | 3.3 | 0.0856 | 0.68 | ( 0.44, 1.06) | 0.67 | ( 0.43, 1.06) | -0.02 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7534 |
| No | 422 | 26 | 6.2 | 408 | 14 | 3.4 | 0.0664 | 0.56 | ( 0.30, 1.05) | 0.54 | ( 0.28, 1.05) | -0.03 | (-0.06, 0.00) | |
| Yes | 766 | 38 | 5.0 | 763 | 24 | 3.1 | 0.0720 | 0.63 | ( 0.38, 1.05) | 0.62 | ( 0.37, 1.05) | -0.02 | (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.0172 |
| No | 629 | 30 | 4.8 | 589 | 26 | 4.4 | 0.7674 | 0.93 | ( 0.55, 1.55) | 0.92 | ( 0.54, 1.58) | 0.00 | (-0.03, 0.02) | |
| Yes | 559 | 34 | 6.1 | 582 | 12 | 2.1 | 0.0006 | 0.34 | ( 0.18, 0.65) | 0.33 | ( 0.17, 0.63) | -0.04 | (-0.06,-0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Endocrine disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 26 | 2.2 | 1171 | 19 | 1.6 | 0.3150 | 0.74 ( 0.41, 1.33) | 0.74 ( 0.41, 1.34) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Immune system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 18 | 1.5 | 1171 | 14 | 1.2 | 0.5023 | 0.79 ( 0.39, 1.58) | 0.79 ( 0.39, 1.59) | 0.00 | (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Surgical and medical procedures

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** | |
| Overall | 1188 | 11 | 0.9 | 1171 | 14 | 1.2 | 0.5225 | 1.29 ( 0.59, 2.83) | 1.29 ( 0.59, 2.86) | 0.00 (-0.01, 0.01) | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 270 | 22.7 | 1171 | 204 | 17.4 | 0.0013 | 0.77 | ( 0.65, 0.90) | 0.72 | ( 0.59, 0.88) | -0.05 | (-0.09,-0.02) | |
| Sex | | | | | | | | | | | | | | 0.8227 |
| Male | 864 | 209 | 24.2 | 837 | 154 | 18.4 | 0.0036 | 0.76 | ( 0.63, 0.92) | 0.71 | ( 0.56, 0.89) | -0.06 | (-0.10,-0.02) | |
| Female | 324 | 61 | 18.8 | 334 | 50 | 15.0 | 0.1865 | 0.80 | ( 0.57, 1.12) | 0.76 | ( 0.50, 1.14) | -0.04 | (-0.10, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.0164 |
| <65 | 569 | 110 | 19.3 | 547 | 101 | 18.5 | 0.7113 | 0.96 | ( 0.75, 1.22) | 0.94 | ( 0.70, 1.28) | -0.01 | (-0.05, 0.04) | |
| >=65 | 619 | 160 | 25.8 | 624 | 103 | 16.5 | <0.0001 | 0.64 | ( 0.51, 0.80) | 0.57 | ( 0.43, 0.75) | -0.09 | (-0.14,-0.05) | |
| Region | | | | | | | | | | | | | | 0.4845 |
| Europe | 468 | 118 | 25.2 | 434 | 89 | 20.5 | 0.0930 | 0.81 | ( 0.64, 1.04) | 0.77 | ( 0.56, 1.05) | -0.05 | (-0.10, 0.01) | |
| North America | 259 | 57 | 22.0 | 241 | 38 | 15.8 | 0.0755 | 0.72 | ( 0.49, 1.04) | 0.66 | ( 0.42, 1.04) | -0.06 | (-0.13, 0.01) | |
| Latin America | 177 | 41 | 23.2 | 191 | 32 | 16.8 | 0.1234 | 0.72 | ( 0.48, 1.09) | 0.67 | ( 0.40, 1.12) | -0.06 | (-0.15, 0.02) | |
| Africa | 50 | 17 | 34.0 | 54 | 8 | 14.8 | 0.0222 | 0.44 | ( 0.21, 0.92) | 0.34 | ( 0.13, 0.87) | -0.19 | (-0.35,-0.03) | |
| Asia | 234 | 37 | 15.8 | 251 | 37 | 14.7 | 0.7431 | 0.93 | ( 0.61, 1.42) | 0.92 | ( 0.56, 1.51) | -0.01 | (-0.07, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0689 |
| <30 | 554 | 119 | 21.5 | 566 | 78 | 13.8 | 0.0007 | 0.64 | ( 0.49, 0.83) | 0.58 | ( 0.43, 0.80) | -0.08 | (-0.12,-0.03) | |
| >=30 | 634 | 151 | 23.8 | 605 | 126 | 20.8 | 0.2066 | 0.87 | ( 0.71, 1.08) | 0.84 | ( 0.64, 1.10) | -0.03 | (-0.08, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1316 |
| <130 | 379 | 92 | 24.3 | 382 | 59 | 15.4 | 0.0023 | 0.64 | ( 0.47, 0.85) | 0.57 | ( 0.40, 0.82) | -0.09 | (-0.14,-0.03) | |
| >=130 | 809 | 178 | 22.0 | 789 | 145 | 18.4 | 0.0712 | 0.84 | ( 0.69, 1.02) | 0.80 | ( 0.62, 1.02) | -0.04 | (-0.08, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2943 |
| <75 | 500 | 122 | 24.4 | 500 | 89 | 17.8 | 0.0105 | 0.73 | ( 0.57, 0.93) | 0.67 | ( 0.49, 0.91) | -0.07 | (-0.12,-0.02) | |
| 75 to <85 | 427 | 89 | 20.8 | 417 | 60 | 14.4 | 0.0139 | 0.69 | ( 0.51, 0.93) | 0.64 | ( 0.45, 0.91) | -0.06 | (-0.12,-0.01) | |
| >=85 | 261 | 59 | 22.6 | 254 | 55 | 21.7 | 0.7948 | 0.96 | ( 0.69, 1.32) | 0.95 | ( 0.62, 1.43) | -0.01 | (-0.08, 0.06) | |
| History of heart failure | | | | | | | | | | | | | | 0.3596 |
| No | 1048 | 210 | 20.0 | 1031 | 164 | 15.9 | 0.0142 | 0.79 | ( 0.66, 0.96) | 0.75 | ( 0.60, 0.95) | -0.04 | (-0.07,-0.01) | |
| Yes | 140 | 60 | 42.9 | 140 | 40 | 28.6 | 0.0126 | 0.67 | ( 0.48, 0.92) | 0.53 | ( 0.32, 0.88) | -0.14 | (-0.25,-0.03) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.7157 |
| <45 | 179 | 53 | 29.6 | 178 | 38 | 21.3 | 0.0733 | 0.72 ( 0.50, 1.03) | 0.65 ( 0.40, 1.04) | -0.08 (-0.17, 0.01) | |
| >=45 | 1009 | 217 | 21.5 | 993 | 166 | 16.7 | 0.0064 | 0.78 ( 0.65, 0.93) | 0.73 ( 0.59, 0.92) | -0.05 (-0.08,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.5126 |
| Normal (<30) | 250 | 54 | 21.6 | 257 | 47 | 18.3 | 0.3506 | 0.85 ( 0.60, 1.20) | 0.81 ( 0.52, 1.26) | -0.03 (-0.10, 0.04) | |
| Microalbuminuria (30 to <=300) | 675 | 150 | 22.2 | 645 | 100 | 15.5 | 0.0018 | 0.70 ( 0.55, 0.88) | 0.64 ( 0.49, 0.85) | -0.07 (-0.11,-0.03) | |
| Macroalbuminuria (>300) | 260 | 66 | 25.4 | 261 | 56 | 21.5 | 0.2897 | 0.85 ( 0.62, 1.15) | 0.80 ( 0.53, 1.21) | -0.04 (-0.11, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.2663 |
| Low, moderate or high | 1018 | 223 | 21.9 | 1001 | 161 | 16.1 | 0.0009 | 0.73 ( 0.61, 0.88) | 0.68 ( 0.55, 0.86) | -0.06 (-0.09,-0.02) | |
| Very high | 167 | 47 | 28.1 | 162 | 42 | 25.9 | 0.6507 | 0.92 ( 0.65, 1.31) | 0.89 ( 0.55, 1.45) | -0.02 (-0.12, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.9492 |
| No | 205 | 40 | 19.5 | 211 | 32 | 15.2 | 0.2414 | 0.78 ( 0.51, 1.19) | 0.74 ( 0.44, 1.23) | -0.04 (-0.12, 0.03) | |
| Yes | 983 | 230 | 23.4 | 960 | 172 | 17.9 | 0.0029 | 0.77 ( 0.64, 0.91) | 0.71 ( 0.57, 0.89) | -0.05 (-0.09,-0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.8143 |
| No | 422 | 72 | 17.1 | 408 | 55 | 13.5 | 0.1519 | 0.79 ( 0.57, 1.09) | 0.76 ( 0.52, 1.11) | -0.04 (-0.08, 0.01) | |
| Yes | 766 | 198 | 25.8 | 763 | 149 | 19.5 | 0.0032 | 0.76 ( 0.63, 0.91) | 0.70 ( 0.55, 0.89) | -0.06 (-0.11,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.4953 |
| No | 629 | 115 | 18.3 | 589 | 76 | 12.9 | 0.0099 | 0.71 ( 0.54, 0.92) | 0.66 ( 0.48, 0.91) | -0.05 (-0.09,-0.01) | |
| Yes | 559 | 155 | 27.7 | 582 | 128 | 22.0 | 0.0249 | 0.79 ( 0.65, 0.97) | 0.73 ( 0.56, 0.96) | -0.06 (-0.11,-0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 160 | 13.5 | 1171 | 139 | 11.9 | 0.2435 | 0.88 ( 0.71, 1.09) | 0.87 ( 0.68, 1.10) | -0.02 (-0.04, 0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 109 | 9.2 | 1171 | 98 | 8.4 | 0.4890 | 0.91 ( 0.70, 1.18) | 0.90 ( 0.68, 1.20) | -0.01 (-0.03, 0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 81 | 6.8 | 1171 | 59 | 5.0 | 0.0674 | 0.74 ( 0.53, 1.02) | 0.73 ( 0.51, 1.02) | -0.02 (-0.04, 0.00) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 73 | 6.1 | 1171 | 57 | 4.9 | 0.1741 | 0.79 ( 0.57, 1.11) | 0.78 ( 0.55, 1.12) | -0.01 (-0.03, 0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 67 | 5.6 | 1171 | 71 | 6.1 | 0.6613 | 1.08 | ( 0.78, 1.49) | 1.08 | ( 0.77, 1.52) | 0.00 | (-0.01, 0.02) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 62 | 5.2 | 1171 | 68 | 5.8 | 0.5314 | 1.11 ( 0.80, 1.55) | 1.12 ( 0.79, 1.60) | 0.01 (-0.01, 0.02) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 66 | 5.6 | 1171 | 54 | 4.6 | 0.2968 | 0.83 ( 0.58, 1.18) | 0.82 ( 0.57, 1.19) | -0.01 (-0.03, 0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 60 | 5.1 | 1171 | 35 | 3.0 | 0.0109 | 0.59 | ( 0.39, | 0.89) | 0.58 | ( 0.38, | 0.89) | -0.02 | (-0.04, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.5571 |
| Male | 864 | 42 | 4.9 | 837 | 26 | 3.1 | 0.0648 | 0.64 | ( 0.40, | 1.03) | 0.63 | ( 0.38, | 1.03) | -0.02 | (-0.04, 0.00) | |
| Female | 324 | 18 | 5.6 | 334 | 9 | 2.7 | 0.0644 | 0.49 | ( 0.22, | 1.06) | 0.47 | ( 0.21, | 1.06) | -0.03 | (-0.06, 0.00) | |
| Age [years] | | | | | | | | | | | | | | | | 0.3688 |
| <65 | 569 | 25 | 4.4 | 547 | 11 | 2.0 | 0.0243 | 0.46 | ( 0.23, | 0.92) | 0.45 | ( 0.22, | 0.92) | -0.02 | (-0.04, 0.00) | |
| >=65 | 619 | 35 | 5.7 | 624 | 24 | 3.8 | 0.1339 | 0.68 | ( 0.41, | 1.13) | 0.67 | ( 0.39, | 1.14) | -0.02 | (-0.04, 0.01) | |
| Region | | | | | | | | | | | | | | | | 0.0755 |
| Europe | 468 | 34 | 7.3 | 434 | 9 | 2.1 | 0.0003 | 0.29 | ( 0.14, | 0.59) | 0.27 | ( 0.13, | 0.57) | -0.05 | (-0.08,-0.02) | |
| North America | 259 | 10 | 3.9 | 241 | 8 | 3.3 | 0.7454 | 0.86 | ( 0.35, | 2.14) | 0.85 | ( 0.33, | 2.20) | -0.01 | (-0.04, 0.03) | |
| Latin America | 177 | 5 | 2.8 | 191 | 6 | 3.1 | 0.8586 | 1.11 | ( 0.35, | 3.58) | 1.12 | ( 0.33, | 3.72) | 0.00 | (-0.03, 0.04) | |
| Africa | 50 | 4 | 8.0 | 54 | 2 | 3.7 | 0.3478 | 0.46 | ( 0.09, | 2.42) | 0.44 | ( 0.08, | 2.53) | -0.04 | (-0.13, 0.05) | |
| Asia | 234 | 7 | 3.0 | 251 | 10 | 4.0 | 0.5525 | 1.33 | ( 0.52, | 3.44) | 1.35 | ( 0.50, | 3.60) | 0.01 | (-0.02, 0.04) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.0132 |
| <30 | 554 | 21 | 3.8 | 566 | 22 | 3.9 | 0.9332 | 1.03 | ( 0.57, | 1.84) | 1.03 | ( 0.56, | 1.89) | 0.00 | (-0.02, 0.02) | |
| >=30 | 634 | 39 | 6.2 | 605 | 13 | 2.1 | 0.0004 | 0.35 | ( 0.19, | 0.65) | 0.34 | ( 0.18, | 0.63) | -0.04 | (-0.06,-0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.6002 |
| <130 | 379 | 18 | 4.7 | 382 | 9 | 2.4 | 0.0743 | 0.50 | ( 0.23, | 1.09) | 0.48 | ( 0.21, | 1.09) | -0.02 | (-0.05, 0.00) | |
| >=130 | 809 | 42 | 5.2 | 789 | 26 | 3.3 | 0.0604 | 0.63 | ( 0.39, | 1.02) | 0.62 | ( 0.38, | 1.03) | -0.02 | (-0.04, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.8660 |
| <75 | 500 | 29 | 5.8 | 500 | 16 | 3.2 | 0.0474 | 0.55 | ( 0.30, | >1.00) | 0.54 | ( 0.29, | 1.00) | -0.03 | (-0.05, 0.00) | |
| 75 to <85 | 427 | 16 | 3.7 | 417 | 11 | 2.6 | 0.3599 | 0.70 | ( 0.33, | 1.50) | 0.70 | ( 0.32, | 1.52) | -0.01 | (-0.03, 0.01) | |
| >=85 | 261 | 15 | 5.7 | 254 | 8 | 3.1 | 0.1536 | 0.55 | ( 0.24, | 1.27) | 0.53 | ( 0.22, | 1.28) | -0.03 | (-0.06, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | | | 0.3968 |
| No | 1048 | 52 | 5.0 | 1031 | 28 | 2.7 | 0.0078 | 0.55 | ( 0.35, | 0.86) | 0.53 | ( 0.33, | 0.85) | -0.02 | (-0.04,-0.01) | |
| Yes | 140 | 8 | 5.7 | 140 | 7 | 5.0 | 0.7907 | 0.88 | ( 0.33, | 2.35) | 0.87 | ( 0.31, | 2.46) | -0.01 | (-0.06, 0.05) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5544 |
| <45 | 179 | 15 | 8.4 | 178 | 7 | 3.9 | 0.0806 | 0.47 | ( 0.20, 1.12) | 0.45 | ( 0.18, 1.13) | -0.04 | (-0.09, 0.01) | |
| >=45 | 1009 | 45 | 4.5 | 993 | 28 | 2.8 | 0.0503 | 0.63 | ( 0.40, 1.01) | 0.62 | ( 0.38, 1.00) | -0.02 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1891 |
| Normal (<30) | 250 | 18 | 7.2 | 257 | 5 | 1.9 | 0.0045 | 0.27 | ( 0.10, 0.72) | 0.26 | ( 0.09, 0.70) | -0.05 | (-0.09,-0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 29 | 4.3 | 645 | 20 | 3.1 | 0.2508 | 0.72 | ( 0.41, 1.26) | 0.71 | ( 0.40, 1.27) | -0.01 | (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 260 | 13 | 5.0 | 261 | 10 | 3.8 | 0.5162 | 0.77 | ( 0.34, 1.72) | 0.76 | ( 0.33, 1.76) | -0.01 | (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1890 |
| Low, moderate or high | 1018 | 48 | 4.7 | 1001 | 24 | 2.4 | 0.0050 | 0.51 | ( 0.31, 0.82) | 0.50 | ( 0.30, 0.82) | -0.02 | (-0.04,-0.01) | |
| Very high | 167 | 12 | 7.2 | 162 | 11 | 6.8 | 0.8881 | 0.94 | ( 0.43, 2.08) | 0.94 | ( 0.40, 2.20) | 0.00 | (-0.06, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7712 |
| No | 205 | 7 | 3.4 | 211 | 5 | 2.4 | 0.5244 | 0.69 | ( 0.22, 2.15) | 0.69 | ( 0.21, 2.20) | -0.01 | (-0.04, 0.02) | |
| Yes | 983 | 53 | 5.4 | 960 | 30 | 3.1 | 0.0135 | 0.58 | ( 0.37, 0.90) | 0.57 | ( 0.36, 0.89) | -0.02 | (-0.04, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4830 |
| No | 422 | 18 | 4.3 | 408 | 8 | 2.0 | 0.0567 | 0.46 | ( 0.20, 1.05) | 0.45 | ( 0.19, 1.04) | -0.02 | (-0.05, 0.00) | |
| Yes | 766 | 42 | 5.5 | 763 | 27 | 3.5 | 0.0671 | 0.65 | ( 0.40, 1.04) | 0.63 | ( 0.39, 1.04) | -0.02 | (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8372 |
| No | 629 | 26 | 4.1 | 589 | 15 | 2.5 | 0.1249 | 0.62 | ( 0.33, 1.15) | 0.61 | ( 0.32, 1.16) | -0.02 | (-0.04, 0.00) | |
| Yes | 559 | 34 | 6.1 | 582 | 20 | 3.4 | 0.0354 | 0.56 | ( 0.33, 0.97) | 0.55 | ( 0.31, 0.97) | -0.03 | (-0.05, 0.00) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 60 | 5.1 | 1171 | 40 | 3.4 | 0.0488 | 0.68 ( 0.46, >1.00) | 0.66 ( 0.44, 1.00) | -0.02 (-0.03, 0.00) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 54 | 4.5 | 1171 | 39 | 3.3 | 0.1295 | 0.73 ( 0.49, 1.10) | 0.72 ( 0.48, 1.10) | -0.01 (-0.03, 0.00) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 51 | 4.3 | 1171 | 42 | 3.6 | 0.3781 | 0.84 ( 0.56, 1.25) | 0.83 ( 0.55, 1.26) | -0.01 (-0.02, 0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 27 | 2.3 | 1171 | 14 | 1.2 | 0.0453 | 0.53 | ( 0.28, <1.00) | 0.52 | ( 0.27, 1.00) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.8170 |
| Male | 864 | 24 | 2.8 | 837 | 12 | 1.4 | 0.0542 | 0.52 | ( 0.26, 1.03) | 0.51 | ( 0.25, 1.02) | -0.01 | (-0.03, 0.00) | |
| Female | 324 | 3 | 0.9 | 334 | 2 | 0.6 | 0.6290 | 0.65 | ( 0.11, 3.85) | 0.64 | ( 0.11, 3.88) | 0.00 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.8651 |
| <65 | 569 | 15 | 2.6 | 547 | 8 | 1.5 | 0.1677 | 0.55 | ( 0.24, 1.30) | 0.55 | ( 0.23, 1.30) | -0.01 | (-0.03, 0.00) | |
| >=65 | 619 | 12 | 1.9 | 624 | 6 | 1.0 | 0.1494 | 0.50 | ( 0.19, 1.31) | 0.49 | ( 0.18, 1.32) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | 0.6028 |
| Europe | 468 | 12 | 2.6 | 434 | 3 | 0.7 | 0.0280 | 0.27 | ( 0.08, 0.95) | 0.26 | ( 0.07, 0.94) | -0.02 | (-0.04, 0.00) | |
| North America | 259 | 2 | 0.8 | 241 | 2 | 0.8 | 0.9423 | 1.07 | ( 0.15, 7.57) | 1.08 | ( 0.15, 7.69) | 0.00 | (-0.02, 0.02) | |
| Latin America | 177 | 7 | 4.0 | 191 | 6 | 3.1 | 0.6728 | 0.79 | ( 0.27, 2.32) | 0.79 | ( 0.26, 2.39) | -0.01 | (-0.05, 0.03) | |
| Africa | 50 | 2 | 4.0 | 54 | 0 | 0 | 0.2155 | 0.19 | (<0.01, 3.77) | 0.18 | (<0.01, 3.80) | -0.04 | (-0.10, 0.02) | |
| Asia | 234 | 4 | 1.7 | 251 | 3 | 1.2 | 0.6352 | 0.70 | ( 0.16, 3.09) | 0.70 | ( 0.15, 3.14) | -0.01 | (-0.03, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2778 |
| <30 | 554 | 14 | 2.5 | 566 | 5 | 0.9 | 0.0332 | 0.35 | ( 0.13, 0.96) | 0.34 | ( 0.12, 0.96) | -0.02 | (-0.03, 0.00) | |
| >=30 | 634 | 13 | 2.1 | 605 | 9 | 1.5 | 0.4533 | 0.73 | ( 0.31, 1.68) | 0.72 | ( 0.31, 1.70) | -0.01 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6207 |
| <130 | 379 | 4 | 1.1 | 382 | 3 | 0.8 | 0.6964 | 0.74 | ( 0.17, 3.30) | 0.74 | ( 0.16, 3.34) | 0.00 | (-0.02, 0.01) | |
| >=130 | 809 | 23 | 2.8 | 789 | 11 | 1.4 | 0.0448 | 0.49 | ( 0.24, <1.00) | 0.48 | ( 0.23, 1.00) | -0.01 | (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0241 |
| <75 | 500 | 6 | 1.2 | 500 | 4 | 0.8 | 0.5250 | 0.67 | ( 0.19, 2.35) | 0.66 | ( 0.19, 2.37) | 0.00 | (-0.02, 0.01) | |
| 75 to <85 | 427 | 16 | 3.7 | 417 | 2 | 0.5 | 0.0010 | 0.13 | ( 0.03, 0.55) | 0.12 | ( 0.03, 0.54) | -0.03 | (-0.05,-0.01) | |
| >=85 | 261 | 5 | 1.9 | 254 | 8 | 3.1 | 0.3721 | 1.64 | ( 0.55, 4.96) | 1.67 | ( 0.54, 5.16) | 0.01 | (-0.01, 0.04) | |
| History of heart failure | | | | | | | | | | | | | | 0.5298 |
| No | 1048 | 21 | 2.0 | 1031 | 12 | 1.2 | 0.1255 | 0.58 | ( 0.29, 1.17) | 0.58 | ( 0.28, 1.18) | -0.01 | (-0.02, 0.00) | |
| Yes | 140 | 6 | 4.3 | 140 | 2 | 1.4 | 0.1513 | 0.33 | ( 0.07, 1.62) | 0.32 | ( 0.06, 1.63) | -0.03 | (-0.07, 0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.8319 |
| <45 | 179 | 5 | 2.8 | 178 | 3 | 1.7 | 0.4795 | 0.60 ( 0.15, 2.49) | 0.60 ( 0.14, 2.53) | -0.01 (-0.04, 0.02) | |
| >=45 | 1009 | 22 | 2.2 | 993 | 11 | 1.1 | 0.0595 | 0.51 ( 0.25, 1.04) | 0.50 ( 0.24, 1.04) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.9970 |
| Normal (<30) | 250 | 2 | 0.8 | 257 | 1 | 0.4 | 0.5464 | 0.49 ( 0.04, 5.33) | 0.48 ( 0.04, 5.38) | 0.00 (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 12 | 1.8 | 645 | 6 | 0.9 | 0.1844 | 0.52 ( 0.20, 1.39) | 0.52 ( 0.19, 1.39) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 260 | 13 | 5.0 | 261 | 7 | 2.7 | 0.1685 | 0.54 ( 0.22, 1.32) | 0.52 ( 0.21, 1.33) | -0.02 (-0.06, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.3168 |
| Low, moderate or high | 1018 | 17 | 1.7 | 1001 | 11 | 1.1 | 0.2726 | 0.66 ( 0.31, 1.40) | 0.65 ( 0.30, 1.40) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 10 | 6.0 | 162 | 3 | 1.9 | 0.0542 | 0.31 ( 0.09, 1.10) | 0.30 ( 0.08, 1.10) | -0.04 (-0.08, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.4563 |
| No | 205 | 4 | 2.0 | 211 | 1 | 0.5 | 0.1669 | 0.24 ( 0.03, 2.15) | 0.24 ( 0.03, 2.16) | -0.01 (-0.04, 0.01) | |
| Yes | 983 | 23 | 2.3 | 960 | 13 | 1.4 | 0.1072 | 0.58 ( 0.29, 1.14) | 0.57 ( 0.29, 1.14) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.1677 |
| No | 422 | 16 | 3.8 | 408 | 5 | 1.2 | 0.0186 | 0.32 ( 0.12, 0.87) | 0.31 ( 0.11, 0.87) | -0.03 (-0.05, 0.00) | |
| Yes | 766 | 11 | 1.4 | 763 | 9 | 1.2 | 0.6590 | 0.82 ( 0.34, 1.97) | 0.82 ( 0.34, 1.99) | 0.00 (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | 0.1762 |
| No | 629 | 14 | 2.2 | 589 | 10 | 1.7 | 0.5076 | 0.76 ( 0.34, 1.70) | 0.76 ( 0.33, 1.72) | -0.01 (-0.02, 0.01) | |
| Yes | 559 | 13 | 2.3 | 582 | 4 | 0.7 | 0.0224 | 0.30 ( 0.10, 0.90) | 0.29 ( 0.09, 0.90) | -0.02 (-0.03, 0.00) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 18 | 1.5 | 1171 | 13 | 1.1 | 0.3878 | 0.73 ( 0.36, 1.49) | 0.73 ( 0.36, 1.50) | 0.00 (-0.01, 0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 12 | 1.0 | 1171 | 17 | 1.5 | 0.3304 | 1.44 ( 0.69, 3.00) | 1.44 ( 0.69, 3.04) | 0.00 ( 0.00, 0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 16 | 1.3 | 1171 | 12 | 1.0 | 0.4702 | 0.76 ( 0.36, 1.60) | 0.76 ( 0.36, 1.61) | 0.00 (-0.01, 0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 13 | 1.1 | 1171 | 14 | 1.2 | 0.8171 | 1.09 ( 0.52, 2.31) | 1.09 ( 0.51, 2.34) | 0.00 (-0.01, 0.01) | |

A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 156 | 13.1 | 1171 | 106 | 9.1 | 0.0016 | 0.69 ( 0.55, 0.87) | 0.66 ( 0.51, 0.85) | -0.04 (-0.07,-0.02) | |
| Sex | | | | | | | | | | | 0.4408 |
| Male | 864 | 124 | 14.4 | 837 | 79 | 9.4 | 0.0018 | 0.66 ( 0.50, 0.86) | 0.62 ( 0.46, 0.84) | -0.05 (-0.08,-0.02) | |
| Female | 324 | 32 | 9.9 | 334 | 27 | 8.1 | 0.4210 | 0.82 ( 0.50, 1.33) | 0.80 ( 0.47, 1.37) | -0.02 (-0.06, 0.03) | |
| Age [years] | | | | | | | | | | | 0.0615 |
| <65 | 569 | 64 | 11.2 | 547 | 54 | 9.9 | 0.4550 | 0.88 ( 0.62, 1.24) | 0.86 ( 0.59, 1.27) | -0.01 (-0.05, 0.02) | |
| >=65 | 619 | 92 | 14.9 | 624 | 52 | 8.3 | 0.0003 | 0.56 ( 0.41, 0.77) | 0.52 ( 0.36, 0.75) | -0.07 (-0.10,-0.03) | |
| Region | | | | | | | | | | | 0.2611 |
| Europe | 468 | 56 | 12.0 | 434 | 40 | 9.2 | 0.1810 | 0.77 ( 0.52, 1.13) | 0.75 ( 0.49, 1.15) | -0.03 (-0.07, 0.01) | |
| North America | 259 | 35 | 13.5 | 241 | 28 | 11.6 | 0.5234 | 0.86 ( 0.54, 1.37) | 0.84 ( 0.49, 1.43) | -0.02 (-0.08, 0.04) | |
| Latin America | 177 | 29 | 16.4 | 191 | 18 | 9.4 | 0.0456 | 0.58 ( 0.33, <1.00) | 0.53 ( 0.28, 0.99) | -0.07 (-0.14, 0.00) | |
| Africa | 50 | 13 | 26.0 | 54 | 3 | 5.6 | 0.0039 | 0.21 ( 0.06, 0.71) | 0.17 ( 0.04, 0.63) | -0.20 (-0.34,-0.07) | |
| Asia | 234 | 23 | 9.8 | 251 | 17 | 6.8 | 0.2215 | 0.69 ( 0.38, 1.26) | 0.67 ( 0.35, 1.28) | -0.03 (-0.08, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.0699 |
| <30 | 554 | 73 | 13.2 | 566 | 40 | 7.1 | 0.0007 | 0.54 ( 0.37, 0.77) | 0.50 ( 0.33, 0.75) | -0.06 (-0.10,-0.03) | |
| >=30 | 634 | 83 | 13.1 | 605 | 66 | 10.9 | 0.2378 | 0.83 ( 0.62, 1.13) | 0.81 ( 0.58, 1.15) | -0.02 (-0.06, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.2769 |
| <130 | 379 | 57 | 15.0 | 382 | 33 | 8.6 | 0.0063 | 0.57 ( 0.38, 0.86) | 0.53 ( 0.34, 0.84) | -0.06 (-0.11,-0.02) | |
| >=130 | 809 | 99 | 12.2 | 789 | 73 | 9.3 | 0.0542 | 0.76 ( 0.57, 1.01) | 0.73 ( 0.53, 1.01) | -0.03 (-0.06, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.1599 |
| <75 | 500 | 70 | 14.0 | 500 | 48 | 9.6 | 0.0310 | 0.69 ( 0.49, 0.97) | 0.65 ( 0.44, 0.96) | -0.04 (-0.08, 0.00) | |
| 75 to <85 | 427 | 56 | 13.1 | 417 | 29 | 7.0 | 0.0029 | 0.53 ( 0.35, 0.81) | 0.50 ( 0.31, 0.79) | -0.06 (-0.10,-0.02) | |
| >=85 | 261 | 30 | 11.5 | 254 | 29 | 11.4 | 0.9781 | 0.99 ( 0.61, 1.61) | 0.99 ( 0.58, 1.71) | 0.00 (-0.06, 0.05) | |
| History of heart failure | | | | | | | | | | | 0.3070 |
| No | 1048 | 121 | 11.5 | 1031 | 87 | 8.4 | 0.0182 | 0.73 ( 0.56, 0.95) | 0.71 ( 0.53, 0.94) | -0.03 (-0.06,-0.01) | |
| Yes | 140 | 35 | 25.0 | 140 | 19 | 13.6 | 0.0154 | 0.54 ( 0.33, 0.90) | 0.47 ( 0.25, 0.87) | -0.11 (-0.21,-0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3797 |
| <45 | 179 | 30 | 16.8 | 178 | 25 | 14.0 | 0.4774 | 0.84 ( 0.51, 1.37) | 0.81 ( 0.46, 1.44) | -0.03 (-0.10, 0.05) | |
| >=45 | 1009 | 126 | 12.5 | 993 | 81 | 8.2 | 0.0015 | 0.65 ( 0.50, 0.85) | 0.62 ( 0.46, 0.84) | -0.04 (-0.07,-0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.5524 |
| Normal (<30) | 250 | 29 | 11.6 | 257 | 25 | 9.7 | 0.4944 | 0.84 ( 0.51, 1.39) | 0.82 ( 0.47, 1.45) | -0.02 (-0.07, 0.04) | |
| Microalbuminuria (30 to <=300) | 675 | 87 | 12.9 | 645 | 51 | 7.9 | 0.0031 | 0.61 ( 0.44, 0.85) | 0.58 ( 0.40, 0.84) | -0.05 (-0.08,-0.02) | |
| Macroalbuminuria (>300) | 260 | 40 | 15.4 | 261 | 30 | 11.5 | 0.1929 | 0.75 ( 0.48, 1.16) | 0.71 ( 0.43, 1.19) | -0.04 (-0.10, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.2107 |
| Low, moderate or high | 1018 | 128 | 12.6 | 1001 | 81 | 8.1 | 0.0009 | 0.64 ( 0.49, 0.84) | 0.61 ( 0.46, 0.82) | -0.04 (-0.07,-0.02) | |
| Very high | 167 | 28 | 16.8 | 162 | 25 | 15.4 | 0.7420 | 0.92 ( 0.56, 1.51) | 0.91 ( 0.50, 1.63) | -0.01 (-0.09, 0.07) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.5387 |
| No | 205 | 24 | 11.7 | 211 | 20 | 9.5 | 0.4599 | 0.81 ( 0.46, 1.42) | 0.79 ( 0.42, 1.48) | -0.02 (-0.08, 0.04) | |
| Yes | 983 | 132 | 13.4 | 960 | 86 | 9.0 | 0.0018 | 0.67 ( 0.52, 0.86) | 0.63 ( 0.48, 0.85) | -0.04 (-0.07,-0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.5860 |
| No | 422 | 42 | 10.0 | 408 | 31 | 7.6 | 0.2312 | 0.76 ( 0.49, 1.19) | 0.74 ( 0.46, 1.21) | -0.02 (-0.06, 0.01) | |
| Yes | 766 | 114 | 14.9 | 763 | 75 | 9.8 | 0.0027 | 0.66 ( 0.50, 0.87) | 0.62 ( 0.46, 0.85) | -0.05 (-0.08,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9360 |
| No | 629 | 59 | 9.4 | 589 | 37 | 6.3 | 0.0449 | 0.67 ( 0.45, 0.99) | 0.65 ( 0.42, 0.99) | -0.03 (-0.06, 0.00) | |
| Yes | 559 | 97 | 17.4 | 582 | 69 | 11.9 | 0.0085 | 0.68 ( 0.51, 0.91) | 0.64 ( 0.46, 0.89) | -0.05 (-0.10,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 100 | 8.4 | 1171 | 79 | 6.7 | 0.1254 | 0.80 ( 0.60, 1.06) | 0.79 ( 0.58, 1.07) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 51 | 4.3 | 1171 | 53 | 4.5 | 0.7827 | 1.05 ( 0.72, 1.54) | 1.06 ( 0.71, 1.57) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 50 | 4.2 | 1171 | 41 | 3.5 | 0.3723 | 0.83 ( 0.55, 1.25) | 0.83 ( 0.54, 1.26) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 35 | 2.9 | 1171 | 43 | 3.7 | 0.3242 | 1.25 ( 0.80, 1.93) | 1.26 ( 0.80, 1.98) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 43 | 3.6 | 1171 | 32 | 2.7 | 0.2196 | 0.75 ( 0.48, 1.18) | 0.75 ( 0.47, 1.19) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 39 | 3.3 | 1171 | 29 | 2.5 | 0.2419 | 0.75 ( 0.47, 1.21) | 0.75 ( 0.46, 1.22) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 33 | 2.8 | 1171 | 38 | 3.2 | 0.5066 | 1.17 ( 0.74, 1.85) | 1.17 ( 0.73, 1.88) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 38 | 3.2 | 1171 | 23 | 2.0 | 0.0589 | 0.61 ( 0.37, 1.02) | 0.61 ( 0.36, 1.02) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 36 | 3.0 | 1171 | 31 | 2.6 | 0.5756 | 0.87 ( 0.54, 1.40) | 0.87 ( 0.53, 1.42) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 28 | 2.4 | 1171 | 21 | 1.8 | 0.3373 | 0.76 ( 0.43, 1.33) | 0.76 ( 0.43, 1.34) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 18 | 1.5 | 1171 | 25 | 2.1 | 0.2606 | 1.41 ( 0.77, 2.57) | 1.42 ( 0.77, 2.61) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 17 | 1.4 | 1171 | 13 | 1.1 | 0.4869 | 0.78 ( 0.38, 1.59) | 0.77 ( 0.37, 1.60) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 14 | 1.2 | 1171 | 7 | 0.6 | 0.1333 | 0.51 ( 0.21, 1.25) | 0.50 ( 0.20, 1.25) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 12 | 1.0 | 1171 | 9 | 0.8 | 0.5323 | 0.76 ( 0.32, 1.80) | 0.76 ( 0.32, 1.81) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.4.2.5**

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 215 | 18.1 | 1171 | 215 | 18.4 | 0.8687 | 1.01 ( 0.86, 1.20) | 1.02 ( 0.83, 1.25) | 0.00 (-0.03, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Upper respiratory tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 112 | 9.4 | 1171 | 106 | 9.1 | 0.7529 | 0.96 ( 0.75, 1.24) | 0.96 ( 0.72, 1.26) | 0.00 (-0.03, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Nasopharyngitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 106 | 8.9 | 1171 | 99 | 8.5 | 0.6865 | 0.95 ( 0.73, 1.23) | 0.94 ( 0.71, 1.26) | 0.00 (-0.03, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Bronchitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 100 | 8.4 | 1171 | 74 | 6.3 | 0.0513 | 0.75 ( 0.56, >1.00) | 0.73 ( 0.54, 1.00) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Influenza

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 85 | 7.2 | 1171 | 66 | 5.6 | 0.1319 | 0.79 ( 0.58, 1.08) | 0.78 ( 0.56, 1.08) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 75 | 6.3 | 1171 | 65 | 5.6 | 0.4333 | 0.88 ( 0.64, 1.21) | 0.87 ( 0.62, 1.23) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Cellulitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 50 | 4.2 | 1171 | 42 | 3.6 | 0.4352 | 0.85 ( 0.57, 1.27) | 0.85 ( 0.56, 1.29) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Gastroenteritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 43 | 3.6 | 1171 | 46 | 3.9 | 0.6940 | 1.09 ( 0.72, 1.63) | 1.09 ( 0.71, 1.66) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Respiratory tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 23 | 1.9 | 1171 | 34 | 2.9 | 0.1260 | 1.50 ( 0.89, 2.53) | 1.51 ( 0.89, 2.59) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Sinusitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 33 | 2.8 | 1171 | 26 | 2.2 | 0.3860 | 0.80 ( 0.48, 1.33) | 0.79 ( 0.47, 1.34) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Asymptomatic bacteriuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 16 | 1.3 | 1171 | 23 | 2.0 | 0.2397 | 1.46 ( 0.77, 2.75) | 1.47 ( 0.77, 2.79) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Onychomycosis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 16 | 1.3 | 1171 | 23 | 2.0 | 0.2397 | 1.46 ( 0.77, 2.75) | 1.47 ( 0.77, 2.79) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pharyngitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 21 | 1.8 | 1171 | 23 | 2.0 | 0.7244 | 1.11 ( 0.62, 2.00) | 1.11 ( 0.61, 2.02) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Herpes zoster

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 20 | 1.7 | 1171 | 18 | 1.5 | 0.7777 | 0.91 ( 0.49, 1.72) | 0.91 ( 0.48, 1.73) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Localised infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 19 | 1.6 | 1171 | 16 | 1.4 | 0.6398 | 0.85 ( 0.44, 1.65) | 0.85 ( 0.44, 1.67) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Erysipelas

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 18 | 1.5 | 0.4514 | 1.30 ( 0.65, 2.61) | 1.31 ( 0.65, 2.64) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Lower respiratory tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 18 | 1.5 | 0.2534 | 1.52 ( 0.74, 3.15) | 1.53 ( 0.73, 3.19) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Gastroenteritis viral

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 18 | 1.5 | 1171 | 12 | 1.0 | 0.2879 | 0.68 ( 0.33, 1.40) | 0.67 ( 0.32, 1.40) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Tinea pedis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 18 | 1.5 | 1171 | 13 | 1.1 | 0.3878 | 0.73 ( 0.36, 1.49) | 0.73 ( 0.36, 1.50) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Cystitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 17 | 1.5 | 0.5600 | 1.23 ( 0.61, 2.49) | 1.24 ( 0.61, 2.52) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Fungal infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 10 | 0.8 | 1171 | 16 | 1.4 | 0.2224 | 1.62 ( 0.74, 3.56) | 1.63 ( 0.74, 3.61) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Conjunctivitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 14 | 1.2 | 0.8825 | 0.95 ( 0.46, 1.95) | 0.95 ( 0.45, 1.97) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Tooth abscess

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 8 | 0.7 | 0.1521 | 0.54 ( 0.23, 1.27) | 0.54 ( 0.23, 1.27) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Rhinitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 11 | 0.9 | 0.5707 | 0.80 ( 0.36, 1.75) | 0.80 ( 0.36, 1.76) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Viral infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 10 | 0.9 | 0.4323 | 0.72 ( 0.32, 1.62) | 0.72 ( 0.32, 1.63) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Wound infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 7 | 0.6 | 1171 | 13 | 1.1 | 0.1677 | 1.88 ( 0.75, 4.71) | 1.89 ( 0.75, 4.76) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Furuncle

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 7 | 0.6 | 1171 | 12 | 1.0 | 0.2367 | 1.74 ( 0.69, 4.40) | 1.75 ( 0.69, 4.45) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Bacteriuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 7 | 0.6 | 0.2626 | 0.59 ( 0.23, 1.50) | 0.59 ( 0.23, 1.50) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypoglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 413 | 34.8 | 1171 | 390 | 33.3 | 0.4545 | 0.96 ( 0.86, | 1.07) | 0.94 ( 0.79, | 1.11) | -0.01 (-0.05, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 256 | 21.5 | 1171 | 142 | 12.1 | <0.0001 | 0.56 ( 0.47, | 0.68) | 0.50 ( 0.40, | 0.63) | -0.09 (-0.12,-0.06) | |
| Sex | | | | | | | | | | | | | 0.0950 |
| Male | 864 | 170 | 19.7 | 837 | 103 | 12.3 | <0.0001 | 0.63 ( 0.50, | 0.78) | 0.57 ( 0.44, | 0.75) | -0.07 (-0.11,-0.04) | |
| Female | 324 | 86 | 26.5 | 334 | 39 | 11.7 | <0.0001 | 0.44 ( 0.31, | 0.62) | 0.37 ( 0.24, | 0.55) | -0.15 (-0.21,-0.09) | |
| Age [years] | | | | | | | | | | | | | 0.9248 |
| <65 | 569 | 134 | 23.6 | 547 | 72 | 13.2 | <0.0001 | 0.56 ( 0.43, | 0.73) | 0.49 ( 0.36, | 0.67) | -0.10 (-0.15,-0.06) | |
| >=65 | 619 | 122 | 19.7 | 624 | 70 | 11.2 | <0.0001 | 0.57 ( 0.43, | 0.75) | 0.51 ( 0.37, | 0.71) | -0.08 (-0.12,-0.04) | |
| Region | | | | | | | | | | | | | 0.6813 |
| Europe | 468 | 120 | 25.6 | 434 | 57 | 13.1 | <0.0001 | 0.51 ( 0.38, | 0.68) | 0.44 ( 0.31, | 0.62) | -0.13 (-0.18,-0.07) | |
| North America | 259 | 32 | 12.4 | 241 | 19 | 7.9 | 0.0988 | 0.64 ( 0.37, | 1.09) | 0.61 ( 0.33, | 1.10) | -0.04 (-0.10, 0.01) | |
| Latin America | 177 | 42 | 23.7 | 191 | 22 | 11.5 | 0.0020 | 0.49 ( 0.30, | 0.78) | 0.42 ( 0.24, | 0.73) | -0.12 (-0.20,-0.04) | |
| Africa | 50 | 8 | 16.0 | 54 | 4 | 7.4 | 0.1706 | 0.46 ( 0.15, | 1.44) | 0.42 ( 0.12, | 1.49) | -0.09 (-0.21, 0.04) | |
| Asia | 234 | 54 | 23.1 | 251 | 40 | 15.9 | 0.0468 | 0.69 ( 0.48, | <1.00) | 0.63 ( 0.40, | 1.00) | -0.07 (-0.14, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.4818 |
| <30 | 554 | 115 | 20.8 | 566 | 71 | 12.5 | 0.0002 | 0.60 ( 0.46, | 0.79) | 0.55 ( 0.40, | 0.76) | -0.08 (-0.13,-0.04) | |
| >=30 | 634 | 141 | 22.2 | 605 | 71 | 11.7 | <0.0001 | 0.53 ( 0.41, | 0.69) | 0.46 ( 0.34, | 0.63) | -0.11 (-0.15,-0.06) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.7543 |
| <130 | 379 | 67 | 17.7 | 382 | 40 | 10.5 | 0.0042 | 0.59 ( 0.41, | 0.85) | 0.54 ( 0.36, | 0.83) | -0.07 (-0.12,-0.02) | |
| >=130 | 809 | 189 | 23.4 | 789 | 102 | 12.9 | <0.0001 | 0.55 ( 0.44, | 0.69) | 0.49 ( 0.37, | 0.63) | -0.10 (-0.14,-0.07) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.7494 |
| <75 | 500 | 93 | 18.6 | 500 | 56 | 11.2 | 0.0010 | 0.60 ( 0.44, | 0.82) | 0.55 ( 0.39, | 0.79) | -0.07 (-0.12,-0.03) | |
| 75 to <85 | 427 | 97 | 22.7 | 417 | 54 | 12.9 | 0.0002 | 0.57 ( 0.42, | 0.77) | 0.51 ( 0.35, | 0.73) | -0.10 (-0.15,-0.05) | |
| >=85 | 261 | 66 | 25.3 | 254 | 32 | 12.6 | 0.0002 | 0.50 ( 0.34, | 0.73) | 0.43 ( 0.27, | 0.68) | -0.13 (-0.19,-0.06) | |
| History of heart failure | | | | | | | | | | | | | 0.4377 |
| No | 1048 | 225 | 21.5 | 1031 | 121 | 11.7 | <0.0001 | 0.55 ( 0.45, | 0.67) | 0.49 ( 0.38, | 0.62) | -0.10 (-0.13,-0.07) | |
| Yes | 140 | 31 | 22.1 | 140 | 21 | 15.0 | 0.1243 | 0.68 ( 0.41, | 1.12) | 0.62 ( 0.34, | 1.14) | -0.07 (-0.16, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.0408 |
| <45 | 179 | 29 | 16.2 | 178 | 26 | 14.6 | 0.6765 | 0.90 ( 0.55, | 1.47) | 0.88 ( 0.50, | 1.57) | -0.02 (-0.09, 0.06) | |
| >=45 | 1009 | 227 | 22.5 | 993 | 116 | 11.7 | <0.0001 | 0.52 ( 0.42, | 0.64) | 0.46 ( 0.36, | 0.58) | -0.11 (-0.14,-0.08) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.7788 |
| Normal (<30) | 250 | 42 | 16.8 | 257 | 21 | 8.2 | 0.0032 | 0.49 ( 0.30, | 0.80) | 0.44 ( 0.25, | 0.77) | -0.09 (-0.14,-0.03) | |
| Microalbuminuria (30 to <=300) | 675 | 147 | 21.8 | 645 | 83 | 12.9 | <0.0001 | 0.59 ( 0.46, | 0.76) | 0.53 ( 0.40, | 0.71) | -0.09 (-0.13,-0.05) | |
| Macroalbuminuria (>300) | 260 | 67 | 25.8 | 261 | 37 | 14.2 | 0.0009 | 0.55 ( 0.38, | 0.79) | 0.48 ( 0.30, | 0.74) | -0.12 (-0.18,-0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.1021 |
| Low, moderate or high | 1018 | 221 | 21.7 | 1001 | 114 | 11.4 | <0.0001 | 0.52 ( 0.43, | 0.65) | 0.46 ( 0.36, | 0.59) | -0.10 (-0.14,-0.07) | |
| Very high | 167 | 35 | 21.0 | 162 | 27 | 16.7 | 0.3197 | 0.80 ( 0.51, | 1.25) | 0.75 ( 0.43, | 1.32) | -0.04 (-0.13, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.0493 |
| No | 205 | 59 | 28.8 | 211 | 23 | 10.9 | <0.0001 | 0.38 ( 0.24, | 0.59) | 0.30 ( 0.18, | 0.51) | -0.18 (-0.25,-0.10) | |
| Yes | 983 | 197 | 20.0 | 960 | 119 | 12.4 | <0.0001 | 0.62 ( 0.50, | 0.76) | 0.56 ( 0.44, | 0.72) | -0.08 (-0.11,-0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.7193 |
| No | 422 | 98 | 23.2 | 408 | 51 | 12.5 | <0.0001 | 0.54 ( 0.39, | 0.73) | 0.47 ( 0.33, | 0.68) | -0.11 (-0.16,-0.06) | |
| Yes | 766 | 158 | 20.6 | 763 | 91 | 11.9 | <0.0001 | 0.58 ( 0.46, | 0.73) | 0.52 ( 0.39, | 0.69) | -0.09 (-0.12,-0.05) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.7395 |
| No | 629 | 146 | 23.2 | 589 | 75 | 12.7 | <0.0001 | 0.55 ( 0.43, | 0.71) | 0.48 ( 0.36, | 0.65) | -0.10 (-0.15,-0.06) | |
| Yes | 559 | 110 | 19.7 | 582 | 67 | 11.5 | 0.0001 | 0.59 ( 0.44, | 0.77) | 0.53 ( 0.38, | 0.74) | -0.08 (-0.12,-0.04) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Dyslipidaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 54 | 4.5 | 1171 | 63 | 5.4 | 0.3506 | 1.18 ( 0.83, | 1.69) | 1.19 ( 0.82, | 1.73) | 0.01 (-0.01, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Diabetes mellitus inadequate control

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 63 | 5.3 | 1171 | 38 | 3.2 | 0.0136 | 0.61 | ( 0.41, 0.91) | 0.60 | ( 0.40, 0.90) | -0.02 | (-0.04, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.1541 |
| Male | 864 | 46 | 5.3 | 837 | 32 | 3.8 | 0.1390 | 0.72 | ( 0.46, 1.12) | 0.71 | ( 0.45, 1.12) | -0.02 | (-0.03, 0.00) | |
| Female | 324 | 17 | 5.2 | 334 | 6 | 1.8 | 0.0160 | 0.34 | ( 0.14, 0.86) | 0.33 | ( 0.13, 0.85) | -0.03 | (-0.06,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.2655 |
| <65 | 569 | 36 | 6.3 | 547 | 17 | 3.1 | 0.0115 | 0.49 | ( 0.28, 0.86) | 0.47 | ( 0.26, 0.86) | -0.03 | (-0.06,-0.01) | |
| >=65 | 619 | 27 | 4.4 | 624 | 21 | 3.4 | 0.3619 | 0.77 | ( 0.44, 1.35) | 0.76 | ( 0.43, 1.37) | -0.01 | (-0.03, 0.01) | |
| Region | | | | | | | | | | | | | | 0.2570 |
| Europe | 468 | 25 | 5.3 | 434 | 9 | 2.1 | 0.0100 | 0.39 | ( 0.18, 0.82) | 0.38 | ( 0.17, 0.81) | -0.03 | (-0.06,-0.01) | |
| North America | 259 | 10 | 3.9 | 241 | 5 | 2.1 | 0.2420 | 0.54 | ( 0.19, 1.55) | 0.53 | ( 0.18, 1.57) | -0.02 | (-0.05, 0.01) | |
| Latin America | 177 | 7 | 4.0 | 191 | 10 | 5.2 | 0.5587 | 1.32 | ( 0.52, 3.40) | 1.34 | ( 0.50, 3.60) | 0.01 | (-0.03, 0.06) | |
| Africa | 50 | 3 | 6.0 | 54 | 0 | 0 | 0.1080 | 0.13 | (<0.01, 2.50) | 0.12 | (<0.01, 2.47) | -0.06 | (-0.13, 0.01) | |
| Asia | 234 | 18 | 7.7 | 251 | 14 | 5.6 | 0.3486 | 0.73 | ( 0.37, 1.42) | 0.71 | ( 0.34, 1.46) | -0.02 | (-0.07, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0583 |
| <30 | 554 | 30 | 5.4 | 566 | 26 | 4.6 | 0.5282 | 0.85 | ( 0.51, 1.42) | 0.84 | ( 0.49, 1.44) | -0.01 | (-0.03, 0.02) | |
| >=30 | 634 | 33 | 5.2 | 605 | 12 | 2.0 | 0.0024 | 0.38 | ( 0.20, 0.73) | 0.37 | ( 0.19, 0.72) | -0.03 | (-0.05,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7471 |
| <130 | 379 | 18 | 4.7 | 382 | 10 | 2.6 | 0.1184 | 0.55 | ( 0.26, 1.18) | 0.54 | ( 0.25, 1.18) | -0.02 | (-0.05, 0.01) | |
| >=130 | 809 | 45 | 5.6 | 789 | 28 | 3.5 | 0.0539 | 0.64 | ( 0.40, 1.01) | 0.62 | ( 0.39, 1.01) | -0.02 | (-0.04, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2206 |
| <75 | 500 | 27 | 5.4 | 500 | 15 | 3.0 | 0.0585 | 0.56 | ( 0.30, 1.03) | 0.54 | ( 0.28, 1.03) | -0.02 | (-0.05, 0.00) | |
| 75 to <85 | 427 | 22 | 5.2 | 417 | 9 | 2.2 | 0.0208 | 0.42 | ( 0.20, 0.90) | 0.41 | ( 0.18, 0.89) | -0.03 | (-0.06, 0.00) | |
| >=85 | 261 | 14 | 5.4 | 254 | 14 | 5.5 | 0.9410 | 1.03 | ( 0.50, 2.11) | 1.03 | ( 0.48, 2.20) | 0.00 | (-0.04, 0.04) | |
| History of heart failure | | | | | | | | | | | | | | 0.5927 |
| No | 1048 | 54 | 5.2 | 1031 | 31 | 3.0 | 0.0135 | 0.58 | ( 0.38, 0.90) | 0.57 | ( 0.36, 0.90) | -0.02 | (-0.04, 0.00) | |
| Yes | 140 | 9 | 6.4 | 140 | 7 | 5.0 | 0.6066 | 0.78 | ( 0.30, 2.03) | 0.77 | ( 0.28, 2.12) | -0.01 | (-0.07, 0.04) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Diabetes mellitus inadequate control

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.9202 |
| <45 | 179 | 12 | 6.7 | 178 | 7 | 3.9 | 0.2435 | 0.59 ( 0.24, | 1.46) | 0.57 ( 0.22, | 1.48) | -0.03 (-0.07, 0.02) | |
| >=45 | 1009 | 51 | 5.1 | 993 | 31 | 3.1 | 0.0291 | 0.62 ( 0.40, | 0.96) | 0.61 ( 0.38, | 0.95) | -0.02 (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.2847 |
| Normal (<30) | 250 | 9 | 3.6 | 257 | 3 | 1.2 | 0.0716 | 0.32 ( 0.09, | 1.18) | 0.32 ( 0.08, | 1.18) | -0.02 (-0.05, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 36 | 5.3 | 645 | 27 | 4.2 | 0.3284 | 0.78 ( 0.48, | 1.28) | 0.78 ( 0.47, | 1.29) | -0.01 (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 260 | 18 | 6.9 | 261 | 8 | 3.1 | 0.0432 | 0.44 ( 0.20, | >1.00) | 0.43 ( 0.18, | 1.00) | -0.04 (-0.08, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.4833 |
| Low, moderate or high | 1018 | 53 | 5.2 | 1001 | 30 | 3.0 | 0.0124 | 0.58 ( 0.37, | 0.89) | 0.56 ( 0.36, | 0.89) | -0.02 (-0.04, 0.00) | |
| Very high | 167 | 10 | 6.0 | 162 | 8 | 4.9 | 0.6755 | 0.82 ( 0.33, | 2.04) | 0.82 ( 0.31, | 2.12) | -0.01 (-0.06, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.1589 |
| No | 205 | 9 | 4.4 | 211 | 10 | 4.7 | 0.8646 | 1.08 ( 0.45, | 2.60) | 1.08 ( 0.43, | 2.72) | 0.00 (-0.04, 0.04) | |
| Yes | 983 | 54 | 5.5 | 960 | 28 | 2.9 | 0.0047 | 0.53 ( 0.34, | 0.83) | 0.52 ( 0.32, | 0.82) | -0.03 (-0.04,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.1051 |
| No | 422 | 27 | 6.4 | 408 | 10 | 2.5 | 0.0059 | 0.38 ( 0.19, | 0.78) | 0.37 ( 0.18, | 0.77) | -0.04 (-0.07,-0.01) | |
| Yes | 766 | 36 | 4.7 | 763 | 28 | 3.7 | 0.3146 | 0.78 ( 0.48, | 1.27) | 0.77 ( 0.47, | 1.28) | -0.01 (-0.03, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.4808 |
| No | 629 | 37 | 5.9 | 589 | 24 | 4.1 | 0.1483 | 0.69 ( 0.42, | 1.14) | 0.68 ( 0.40, | 1.15) | -0.02 (-0.04, 0.01) | |
| Yes | 559 | 26 | 4.7 | 582 | 14 | 2.4 | 0.0392 | 0.52 ( 0.27, | 0.98) | 0.51 ( 0.26, | 0.98) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperkalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 56 | 4.7 | 1171 | 26 | 2.2 | 0.0009 | 0.47 | ( 0.30, 0.74) | 0.46 | ( 0.29, 0.74) | -0.02 | (-0.04,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.5415 |
| Male | 864 | 39 | 4.5 | 837 | 16 | 1.9 | 0.0024 | 0.42 | ( 0.24, 0.75) | 0.41 | ( 0.23, 0.74) | -0.03 | (-0.04,-0.01) | |
| Female | 324 | 17 | 5.2 | 334 | 10 | 3.0 | 0.1453 | 0.57 | ( 0.27, 1.23) | 0.56 | ( 0.25, 1.24) | -0.02 | (-0.05, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.5105 |
| <65 | 569 | 22 | 3.9 | 547 | 8 | 1.5 | 0.0131 | 0.38 | ( 0.17, 0.84) | 0.37 | ( 0.16, 0.84) | -0.02 | (-0.04,-0.01) | |
| >=65 | 619 | 34 | 5.5 | 624 | 18 | 2.9 | 0.0217 | 0.53 | ( 0.30, 0.92) | 0.51 | ( 0.29, 0.92) | -0.03 | (-0.05, 0.00) | |
| Region | | | | | | | | | | | | | | 0.4637 |
| Europe | 468 | 12 | 2.6 | 434 | 9 | 2.1 | 0.6256 | 0.81 | ( 0.34, 1.90) | 0.80 | ( 0.34, 1.93) | 0.00 | (-0.02, 0.01) | |
| North America | 259 | 14 | 5.4 | 241 | 7 | 2.9 | 0.1636 | 0.54 | ( 0.22, 1.31) | 0.52 | ( 0.21, 1.32) | -0.03 | (-0.06, 0.01) | |
| Latin America | 177 | 11 | 6.2 | 191 | 5 | 2.6 | 0.0909 | 0.42 | ( 0.15, 1.19) | 0.41 | ( 0.14, 1.19) | -0.04 | (-0.08, 0.01) | |
| Africa | 50 | 2 | 4.0 | 54 | 1 | 1.9 | 0.5131 | 0.46 | ( 0.04, 4.95) | 0.45 | ( 0.04, 5.15) | -0.02 | (-0.09, 0.04) | |
| Asia | 234 | 17 | 7.3 | 251 | 4 | 1.6 | 0.0022 | 0.22 | ( 0.07, 0.64) | 0.21 | ( 0.07, 0.62) | -0.06 | (-0.09,-0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7177 |
| <30 | 554 | 29 | 5.2 | 566 | 15 | 2.7 | 0.0260 | 0.51 | ( 0.27, 0.93) | 0.49 | ( 0.26, 0.93) | -0.03 | (-0.05, 0.00) | |
| >=30 | 634 | 27 | 4.3 | 605 | 11 | 1.8 | 0.0128 | 0.43 | ( 0.21, 0.85) | 0.42 | ( 0.20, 0.85) | -0.02 | (-0.04,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6999 |
| <130 | 379 | 17 | 4.5 | 382 | 7 | 1.8 | 0.0363 | 0.41 | ( 0.17, 0.97) | 0.40 | ( 0.16, 0.97) | -0.03 | (-0.05, 0.00) | |
| >=130 | 809 | 39 | 4.8 | 789 | 19 | 2.4 | 0.0099 | 0.50 | ( 0.29, 0.86) | 0.49 | ( 0.28, 0.85) | -0.02 | (-0.04,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7088 |
| <75 | 500 | 29 | 5.8 | 500 | 15 | 3.0 | 0.0309 | 0.52 | ( 0.28, 0.95) | 0.50 | ( 0.27, 0.95) | -0.03 | (-0.05, 0.00) | |
| 75 to <85 | 427 | 18 | 4.2 | 417 | 6 | 1.4 | 0.0153 | 0.34 | ( 0.14, 0.85) | 0.33 | ( 0.13, 0.84) | -0.03 | (-0.05,-0.01) | |
| >=85 | 261 | 9 | 3.4 | 254 | 5 | 2.0 | 0.3019 | 0.57 | ( 0.19, 1.68) | 0.56 | ( 0.19, 1.70) | -0.01 | (-0.04, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.5795 |
| No | 1048 | 48 | 4.6 | 1031 | 21 | 2.0 | 0.0012 | 0.44 | ( 0.27, 0.74) | 0.43 | ( 0.26, 0.73) | -0.03 | (-0.04,-0.01) | |
| Yes | 140 | 8 | 5.7 | 140 | 5 | 3.6 | 0.3942 | 0.63 | ( 0.21, 1.86) | 0.61 | ( 0.19, 1.92) | -0.02 | (-0.07, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperkalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.6666 |
| <45 | 179 | 13 | 7.3 | 178 | 5 | 2.8 | 0.0545 | 0.39 ( 0.14, | 1.06) | 0.37 ( 0.13, | 1.06) | -0.04 (-0.09, 0.00) | |
| >=45 | 1009 | 43 | 4.3 | 993 | 21 | 2.1 | 0.0063 | 0.50 ( 0.30, | 0.83) | 0.49 ( 0.29, | 0.82) | -0.02 (-0.04,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.7758 |
| Normal (<30) | 250 | 12 | 4.8 | 257 | 6 | 2.3 | 0.1337 | 0.49 ( 0.19, | 1.28) | 0.47 ( 0.18, | 1.28) | -0.02 (-0.06, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 29 | 4.3 | 645 | 14 | 2.2 | 0.0297 | 0.51 ( 0.27, | 0.95) | 0.49 ( 0.26, | 0.94) | -0.02 (-0.04, 0.00) | |
| Macroalbuminuria (>300) | 260 | 15 | 5.8 | 261 | 5 | 1.9 | 0.0221 | 0.33 ( 0.12, | 0.90) | 0.32 ( 0.11, | 0.89) | -0.04 (-0.07,-0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.7977 |
| Low, moderate or high | 1018 | 46 | 4.5 | 1001 | 20 | 2.0 | 0.0014 | 0.44 ( 0.26, | 0.74) | 0.43 ( 0.25, | 0.73) | -0.03 (-0.04,-0.01) | |
| Very high | 167 | 10 | 6.0 | 162 | 5 | 3.1 | 0.2072 | 0.52 ( 0.18, | 1.48) | 0.50 ( 0.17, | 1.50) | -0.03 (-0.07, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.2847 |
| No | 205 | 14 | 6.8 | 211 | 4 | 1.9 | 0.0134 | 0.28 ( 0.09, | 0.83) | 0.26 ( 0.09, | 0.81) | -0.05 (-0.09,-0.01) | |
| Yes | 983 | 42 | 4.3 | 960 | 22 | 2.3 | 0.0144 | 0.54 ( 0.32, | 0.89) | 0.53 ( 0.31, | 0.89) | -0.02 (-0.04, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.3267 |
| No | 422 | 12 | 2.8 | 408 | 8 | 2.0 | 0.4070 | 0.69 ( 0.28, | 1.67) | 0.68 ( 0.28, | 1.69) | -0.01 (-0.03, 0.01) | |
| Yes | 766 | 44 | 5.7 | 763 | 18 | 2.4 | 0.0008 | 0.41 ( 0.24, | 0.70) | 0.40 ( 0.23, | 0.69) | -0.03 (-0.05,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.4012 |
| No | 629 | 24 | 3.8 | 589 | 13 | 2.2 | 0.1022 | 0.58 ( 0.30, | 1.13) | 0.57 ( 0.29, | 1.13) | -0.02 (-0.04, 0.00) | |
| Yes | 559 | 32 | 5.7 | 582 | 13 | 2.2 | 0.0025 | 0.39 ( 0.21, | 0.74) | 0.38 ( 0.20, | 0.72) | -0.03 (-0.06,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 43 | 3.6 | 1171 | 19 | 1.6 | 0.0024 | 0.45 ( 0.26, | 0.76) | 0.44 ( 0.25, | 0.76) | -0.02 (-0.03,-0.01) | |
| Sex | | | | | | | | | | | | | 0.1513 |
| Male | 864 | 29 | 3.4 | 837 | 16 | 1.9 | 0.0634 | 0.57 ( 0.31, | 1.04) | 0.56 ( 0.30, | 1.04) | -0.01 (-0.03, 0.00) | |
| Female | 324 | 14 | 4.3 | 334 | 3 | 0.9 | 0.0057 | 0.21 ( 0.06, | 0.72) | 0.20 ( 0.06, | 0.71) | -0.03 (-0.06,-0.01) | |
| Age [years] | | | | | | | | | | | | | 0.8482 |
| <65 | 569 | 22 | 3.9 | 547 | 9 | 1.6 | 0.0240 | 0.43 ( 0.20, | 0.92) | 0.42 ( 0.19, | 0.91) | -0.02 (-0.04, 0.00) | |
| >=65 | 619 | 21 | 3.4 | 624 | 10 | 1.6 | 0.0430 | 0.47 ( 0.22, | 0.99) | 0.46 ( 0.22, | 0.99) | -0.02 (-0.04, 0.00) | |
| Region | | | | | | | | | | | | | 0.4563 |
| Europe | 468 | 16 | 3.4 | 434 | 4 | 0.9 | 0.0109 | 0.27 ( 0.09, | 0.80) | 0.26 ( 0.09, | 0.79) | -0.02 (-0.04,-0.01) | |
| North America | 259 | 6 | 2.3 | 241 | 1 | 0.4 | 0.0705 | 0.18 ( 0.02, | 1.48) | 0.18 ( 0.02, | 1.47) | -0.02 (-0.04, 0.00) | |
| Latin America | 177 | 17 | 9.6 | 191 | 11 | 5.8 | 0.1645 | 0.60 ( 0.29, | 1.24) | 0.58 ( 0.26, | 1.26) | -0.04 (-0.09, 0.02) | |
| Africa | 50 | 1 | 2.0 | 54 | 2 | 3.7 | 0.6040 | 1.85 ( 0.17, | 19.80) | 1.88 ( 0.17, | 21.45) | 0.02 (-0.05, 0.08) | |
| Asia | 234 | 3 | 1.3 | 251 | 1 | 0.4 | 0.2823 | 0.31 ( 0.03, | 2.97) | 0.31 ( 0.03, | 2.98) | -0.01 (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.9160 |
| <30 | 554 | 18 | 3.2 | 566 | 8 | 1.4 | 0.0414 | 0.44 ( 0.19, | 0.99) | 0.43 ( 0.18, | 0.99) | -0.02 (-0.04, 0.00) | |
| >=30 | 634 | 25 | 3.9 | 605 | 11 | 1.8 | 0.0260 | 0.46 ( 0.23, | 0.93) | 0.45 ( 0.22, | 0.93) | -0.02 (-0.04, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.4233 |
| <130 | 379 | 13 | 3.4 | 382 | 4 | 1.0 | 0.0261 | 0.31 ( 0.10, | 0.93) | 0.30 ( 0.10, | 0.92) | -0.02 (-0.04, 0.00) | |
| >=130 | 809 | 30 | 3.7 | 789 | 15 | 1.9 | 0.0290 | 0.51 ( 0.28, | 0.95) | 0.50 ( 0.27, | 0.94) | -0.02 (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.8166 |
| <75 | 500 | 19 | 3.8 | 500 | 7 | 1.4 | 0.0171 | 0.37 ( 0.16, | 0.87) | 0.36 ( 0.15, | 0.86) | -0.02 (-0.04, 0.00) | |
| 75 to <85 | 427 | 11 | 2.6 | 417 | 6 | 1.4 | 0.2397 | 0.56 ( 0.21, | 1.50) | 0.55 ( 0.20, | 1.51) | -0.01 (-0.03, 0.01) | |
| >=85 | 261 | 13 | 5.0 | 254 | 6 | 2.4 | 0.1150 | 0.47 ( 0.18, | 1.23) | 0.46 ( 0.17, | 1.23) | -0.03 (-0.06, 0.01) | |
| History of heart failure | | | | | | | | | | | | | 0.3795 |
| No | 1048 | 32 | 3.1 | 1031 | 16 | 1.6 | 0.0226 | 0.51 ( 0.28, | 0.92) | 0.50 ( 0.27, | 0.92) | -0.02 (-0.03, 0.00) | |
| Yes | 140 | 11 | 7.9 | 140 | 3 | 2.1 | 0.0283 | 0.27 ( 0.08, | 0.96) | 0.26 ( 0.07, | 0.94) | -0.06 (-0.11,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.1926 |
| <45 | 179 | 8 | 4.5 | 178 | 1 | 0.6 | 0.0185 | 0.13 ( 0.02, | 0.99) | 0.12 ( 0.01, | 0.98) | -0.04 (-0.07,-0.01) | |
| >=45 | 1009 | 35 | 3.5 | 993 | 18 | 1.8 | 0.0210 | 0.52 ( 0.30, | 0.92) | 0.51 ( 0.29, | 0.91) | -0.02 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.8885 |
| Normal (<30) | 250 | 9 | 3.6 | 257 | 4 | 1.6 | 0.1455 | 0.43 ( 0.13, | 1.39) | 0.42 ( 0.13, | 1.39) | -0.02 (-0.05, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 21 | 3.1 | 645 | 8 | 1.2 | 0.0205 | 0.40 ( 0.18, | 0.89) | 0.39 ( 0.17, | 0.89) | -0.02 (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 260 | 13 | 5.0 | 261 | 7 | 2.7 | 0.1685 | 0.54 ( 0.22, | 1.32) | 0.52 ( 0.21, | 1.33) | -0.02 (-0.06, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.1546 |
| Low, moderate or high | 1018 | 34 | 3.3 | 1001 | 18 | 1.8 | 0.0288 | 0.54 ( 0.31, | 0.95) | 0.53 ( 0.30, | 0.94) | -0.02 (-0.03, 0.00) | |
| Very high | 167 | 9 | 5.4 | 162 | 1 | 0.6 | 0.0117 | 0.11 ( 0.01, | 0.89) | 0.11 ( 0.01, | 0.87) | -0.05 (-0.08,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.7026 |
| No | 205 | 7 | 3.4 | 211 | 4 | 1.9 | 0.3344 | 0.56 ( 0.17, | 1.87) | 0.55 ( 0.16, | 1.90) | -0.02 (-0.05, 0.02) | |
| Yes | 983 | 36 | 3.7 | 960 | 15 | 1.6 | 0.0038 | 0.43 ( 0.24, | 0.77) | 0.42 ( 0.23, | 0.77) | -0.02 (-0.04,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.8054 |
| No | 422 | 17 | 4.0 | 408 | 8 | 2.0 | 0.0814 | 0.49 ( 0.21, | 1.12) | 0.48 ( 0.20, | 1.12) | -0.02 (-0.04, 0.00) | |
| Yes | 766 | 26 | 3.4 | 763 | 11 | 1.4 | 0.0130 | 0.42 ( 0.21, | 0.85) | 0.42 ( 0.20, | 0.85) | -0.02 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.7969 |
| No | 629 | 20 | 3.2 | 589 | 9 | 1.5 | 0.0588 | 0.48 ( 0.22, | 1.05) | 0.47 ( 0.21, | 1.05) | -0.02 (-0.03, 0.00) | |
| Yes | 559 | 23 | 4.1 | 582 | 10 | 1.7 | 0.0158 | 0.42 ( 0.20, | 0.87) | 0.41 ( 0.19, | 0.86) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Gout

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 29 | 2.4 | 1171 | 38 | 3.2 | 0.2399 | 1.33 ( 0.83, 2.14) | 1.34 ( 0.82, 2.19) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperuricaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 34 | 2.9 | 1171 | 35 | 3.0 | 0.8548 | 1.04 ( 0.66, 1.66) | 1.05 ( 0.65, 1.69) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypomagnesaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 32 | 2.7 | 1171 | 14 | 1.2 | 0.0085 | 0.44 | ( 0.24, 0.83) | 0.44 | ( 0.23, 0.82) | -0.01 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.3647 |
| Male | 864 | 21 | 2.4 | 837 | 7 | 0.8 | 0.0098 | 0.34 | ( 0.15, 0.81) | 0.34 | ( 0.14, 0.80) | -0.02 | (-0.03, 0.00) | |
| Female | 324 | 11 | 3.4 | 334 | 7 | 2.1 | 0.3070 | 0.62 | ( 0.24, 1.57) | 0.61 | ( 0.23, 1.59) | -0.01 | (-0.04, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.1751 |
| <65 | 569 | 14 | 2.5 | 547 | 3 | 0.5 | 0.0091 | 0.22 | ( 0.06, 0.77) | 0.22 | ( 0.06, 0.76) | -0.02 | (-0.03, 0.00) | |
| >=65 | 619 | 18 | 2.9 | 624 | 11 | 1.8 | 0.1811 | 0.61 | ( 0.29, 1.27) | 0.60 | ( 0.28, 1.28) | -0.01 | (-0.03, 0.01) | |
| Region | | | | | | | | | | | | | | 0.4320 |
| Europe | 468 | 10 | 2.1 | 434 | 5 | 1.2 | 0.2479 | 0.54 | ( 0.19, 1.56) | 0.53 | ( 0.18, 1.57) | -0.01 | (-0.03, 0.01) | |
| North America | 259 | 5 | 1.9 | 241 | 5 | 2.1 | 0.9084 | 1.07 | ( 0.32, 3.67) | 1.08 | ( 0.31, 3.76) | 0.00 | (-0.02, 0.03) | |
| Latin America | 177 | 6 | 3.4 | 191 | 1 | 0.5 | 0.0443 | 0.15 | ( 0.02, 1.27) | 0.15 | ( 0.02, 1.26) | -0.03 | (-0.06, 0.00) | |
| Africa | 50 | 3 | 6.0 | 54 | 1 | 1.9 | 0.2717 | 0.31 | ( 0.03, 2.87) | 0.30 | ( 0.03, 2.94) | -0.04 | (-0.12, 0.03) | |
| Asia | 234 | 8 | 3.4 | 251 | 2 | 0.8 | 0.0423 | 0.23 | ( 0.05, 1.09) | 0.23 | ( 0.05, 1.08) | -0.03 | (-0.05, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8705 |
| <30 | 554 | 14 | 2.5 | 566 | 6 | 1.1 | 0.0638 | 0.42 | ( 0.16, 1.08) | 0.41 | ( 0.16, 1.08) | -0.01 | (-0.03, 0.00) | |
| >=30 | 634 | 18 | 2.8 | 605 | 8 | 1.3 | 0.0626 | 0.47 | ( 0.20, 1.06) | 0.46 | ( 0.20, 1.06) | -0.02 | (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6389 |
| <130 | 379 | 9 | 2.4 | 382 | 5 | 1.3 | 0.2740 | 0.55 | ( 0.19, 1.63) | 0.55 | ( 0.18, 1.64) | -0.01 | (-0.03, 0.01) | |
| >=130 | 809 | 23 | 2.8 | 789 | 9 | 1.1 | 0.0152 | 0.40 | ( 0.19, 0.86) | 0.39 | ( 0.18, 0.86) | -0.02 | (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3764 |
| <75 | 500 | 11 | 2.2 | 500 | 8 | 1.6 | 0.4871 | 0.73 | ( 0.30, 1.79) | 0.72 | ( 0.29, 1.81) | -0.01 | (-0.02, 0.01) | |
| 75 to <85 | 427 | 14 | 3.3 | 417 | 4 | 1.0 | 0.0197 | 0.29 | ( 0.10, 0.88) | 0.29 | ( 0.09, 0.88) | -0.02 | (-0.04, 0.00) | |
| >=85 | 261 | 7 | 2.7 | 254 | 2 | 0.8 | 0.1009 | 0.29 | ( 0.06, 1.40) | 0.29 | ( 0.06, 1.40) | -0.02 | (-0.04, 0.00) | |
| History of heart failure | | | | | | | | | | | | | | 0.8920 |
| No | 1048 | 27 | 2.6 | 1031 | 12 | 1.2 | 0.0176 | 0.45 | ( 0.23, 0.89) | 0.45 | ( 0.22, 0.88) | -0.01 | (-0.03, 0.00) | |
| Yes | 140 | 5 | 3.6 | 140 | 2 | 1.4 | 0.2508 | 0.40 | ( 0.08, 2.03) | 0.39 | ( 0.07, 2.05) | -0.02 | (-0.06, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypomagnesaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.7029 |
| <45 | 179 | 6 | 3.4 | 178 | 2 | 1.1 | 0.1549 | 0.34 ( 0.07, | 1.64) | 0.33 ( 0.07, | 1.65) | -0.02 (-0.05, 0.01) | |
| >=45 | 1009 | 26 | 2.6 | 993 | 12 | 1.2 | 0.0249 | 0.47 ( 0.24, | 0.92) | 0.46 ( 0.23, | 0.92) | -0.01 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.4177 |
| Normal (<30) | 250 | 6 | 2.4 | 257 | 5 | 1.9 | 0.7255 | 0.81 ( 0.25, | 2.62) | 0.81 ( 0.24, | 2.68) | 0.00 (-0.03, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 18 | 2.7 | 645 | 5 | 0.8 | 0.0087 | 0.29 ( 0.11, | 0.78) | 0.29 ( 0.11, | 0.77) | -0.02 (-0.03,-0.01) | |
| Macroalbuminuria (>300) | 260 | 8 | 3.1 | 261 | 4 | 1.5 | 0.2400 | 0.50 ( 0.15, | 1.63) | 0.49 ( 0.15, | 1.65) | -0.02 (-0.04, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.3352 |
| Low, moderate or high | 1018 | 26 | 2.6 | 1001 | 13 | 1.3 | 0.0405 | 0.51 ( 0.26, | 0.98) | 0.50 ( 0.26, | 0.98) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 6 | 3.6 | 162 | 1 | 0.6 | 0.0615 | 0.17 ( 0.02, | 1.41) | 0.17 ( 0.02, | 1.40) | -0.03 (-0.06, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.0925 |
| No | 205 | 9 | 4.4 | 211 | 0 | 0 | 0.0034 | 0.05 (<0.01, | 0.87) | 0.05 (<0.01, | 0.85) | -0.04 (-0.07,-0.01) | |
| Yes | 983 | 23 | 2.3 | 960 | 14 | 1.5 | 0.1552 | 0.62 ( 0.32, | 1.20) | 0.62 ( 0.32, | 1.21) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.2105 |
| No | 422 | 8 | 1.9 | 408 | 6 | 1.5 | 0.6344 | 0.78 ( 0.27, | 2.22) | 0.77 ( 0.27, | 2.25) | 0.00 (-0.02, 0.01) | |
| Yes | 766 | 24 | 3.1 | 763 | 8 | 1.0 | 0.0044 | 0.33 ( 0.15, | 0.74) | 0.33 ( 0.15, | 0.73) | -0.02 (-0.04,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.2297 |
| No | 629 | 13 | 2.1 | 589 | 8 | 1.4 | 0.3425 | 0.66 ( 0.27, | 1.57) | 0.65 ( 0.27, | 1.59) | -0.01 (-0.02, 0.01) | |
| Yes | 559 | 19 | 3.4 | 582 | 6 | 1.0 | 0.0063 | 0.30 ( 0.12, | 0.75) | 0.30 ( 0.12, | 0.75) | -0.02 (-0.04,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypertriglyceridaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 27 | 2.3 | 1171 | 9 | 0.8 | 0.0029 | 0.34 | ( 0.16, 0.72) | 0.33 | ( 0.16, 0.71) | -0.02 | (-0.02,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.2620 |
| Male | 864 | 23 | 2.7 | 837 | 6 | 0.7 | 0.0019 | 0.27 | ( 0.11, 0.66) | 0.26 | ( 0.11, 0.65) | -0.02 | (-0.03,-0.01) | |
| Female | 324 | 4 | 1.2 | 334 | 3 | 0.9 | 0.6741 | 0.73 | ( 0.16, 3.23) | 0.73 | ( 0.16, 3.27) | 0.00 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.1244 |
| <65 | 569 | 20 | 3.5 | 547 | 4 | 0.7 | 0.0014 | 0.21 | ( 0.07, 0.60) | 0.20 | ( 0.07, 0.60) | -0.03 | (-0.04,-0.01) | |
| >=65 | 619 | 7 | 1.1 | 624 | 5 | 0.8 | 0.5524 | 0.71 | ( 0.23, 2.22) | 0.71 | ( 0.22, 2.24) | 0.00 | (-0.01, 0.01) | |
| Region | | | | | | | | | | | | | | 0.9961 |
| Europe | 468 | 9 | 1.9 | 434 | 3 | 0.7 | 0.1067 | 0.36 | ( 0.10, 1.32) | 0.35 | ( 0.10, 1.32) | -0.01 | (-0.03, 0.00) | |
| North America | 259 | 1 | 0.4 | 241 | 0 | 0 | 0.5105 | 0.36 | ( 0.01, 8.75) | 0.36 | ( 0.01, 8.80) | 0.00 | (-0.01, 0.01) | |
| Latin America | 177 | 10 | 5.6 | 191 | 3 | 1.6 | 0.0342 | 0.28 | ( 0.08, 0.99) | 0.27 | ( 0.07, 0.98) | -0.04 | (-0.08, 0.00) | |
| Africa | 50 | 2 | 4.0 | 54 | 1 | 1.9 | 0.5131 | 0.46 | ( 0.04, 4.95) | 0.45 | ( 0.04, 5.15) | -0.02 | (-0.09, 0.04) | |
| Asia | 234 | 5 | 2.1 | 251 | 2 | 0.8 | 0.2163 | 0.37 | ( 0.07, 1.90) | 0.37 | ( 0.07, 1.91) | -0.01 | (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9294 |
| <30 | 554 | 15 | 2.7 | 566 | 5 | 0.9 | 0.0212 | 0.33 | ( 0.12, 0.89) | 0.32 | ( 0.12, 0.89) | -0.02 | (-0.03, 0.00) | |
| >=30 | 634 | 12 | 1.9 | 605 | 4 | 0.7 | 0.0549 | 0.35 | ( 0.11, 1.08) | 0.34 | ( 0.11, 1.08) | -0.01 | (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6619 |
| <130 | 379 | 11 | 2.9 | 382 | 3 | 0.8 | 0.0298 | 0.27 | ( 0.08, 0.96) | 0.26 | ( 0.07, 0.96) | -0.02 | (-0.04, 0.00) | |
| >=130 | 809 | 16 | 2.0 | 789 | 6 | 0.8 | 0.0368 | 0.38 | ( 0.15, 0.98) | 0.38 | ( 0.15, 0.98) | -0.01 | (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5610 |
| <75 | 500 | 9 | 1.8 | 500 | 2 | 0.4 | 0.0338 | 0.22 | ( 0.05, 1.02) | 0.22 | ( 0.05, 1.02) | -0.01 | (-0.03, 0.00) | |
| 75 to <85 | 427 | 11 | 2.6 | 417 | 3 | 0.7 | 0.0347 | 0.28 | ( 0.08, 0.99) | 0.27 | ( 0.08, 0.99) | -0.02 | (-0.04, 0.00) | |
| >=85 | 261 | 7 | 2.7 | 254 | 4 | 1.6 | 0.3849 | 0.59 | ( 0.17, 1.98) | 0.58 | ( 0.17, 2.01) | -0.01 | (-0.04, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.4181 |
| No | 1048 | 24 | 2.3 | 1031 | 7 | 0.7 | 0.0024 | 0.30 | ( 0.13, 0.69) | 0.29 | ( 0.13, 0.68) | -0.02 | (-0.03,-0.01) | |
| Yes | 140 | 3 | 2.1 | 140 | 2 | 1.4 | 0.6518 | 0.67 | ( 0.11, 3.93) | 0.66 | ( 0.11, 4.02) | -0.01 | (-0.04, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypertriglyceridaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.4090 |
| <45 | 179 | 4 | 2.2 | 178 | 0 | 0 | 0.0726 | 0.11 (<0.01, | 2.06) | 0.11 (<0.01, | 2.04) | -0.02 (-0.05, 0.00) | |
| >=45 | 1009 | 23 | 2.3 | 993 | 9 | 0.9 | 0.0143 | 0.40 ( 0.18, | 0.85) | 0.39 ( 0.18, | 0.85) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.5334 |
| Normal (<30) | 250 | 2 | 0.8 | 257 | 2 | 0.8 | 0.9779 | 0.97 ( 0.14, | 6.85) | 0.97 ( 0.14, | 6.96) | 0.00 (-0.02, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 18 | 2.7 | 645 | 5 | 0.8 | 0.0087 | 0.29 ( 0.11, | 0.78) | 0.29 ( 0.11, | 0.77) | -0.02 (-0.03,-0.01) | |
| Macroalbuminuria (>300) | 260 | 7 | 2.7 | 261 | 2 | 0.8 | 0.0916 | 0.28 ( 0.06, | 1.36) | 0.28 ( 0.06, | 1.36) | -0.02 (-0.04, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.4177 |
| Low, moderate or high | 1018 | 23 | 2.3 | 1001 | 9 | 0.9 | 0.0144 | 0.40 ( 0.19, | 0.86) | 0.39 ( 0.18, | 0.85) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 4 | 2.4 | 162 | 0 | 0 | 0.0769 | 0.11 (<0.01, | 2.11) | 0.11 (<0.01, | 2.09) | -0.02 (-0.05, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.5769 |
| No | 205 | 5 | 2.4 | 211 | 1 | 0.5 | 0.0928 | 0.19 ( 0.02, | 1.65) | 0.19 ( 0.02, | 1.64) | -0.02 (-0.04, 0.00) | |
| Yes | 983 | 22 | 2.2 | 960 | 8 | 0.8 | 0.0120 | 0.37 ( 0.17, | 0.83) | 0.37 ( 0.16, | 0.83) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.1557 |
| No | 422 | 8 | 1.9 | 408 | 5 | 1.2 | 0.4369 | 0.65 ( 0.21, | 1.96) | 0.64 ( 0.21, | 1.98) | -0.01 (-0.02, 0.01) | |
| Yes | 766 | 19 | 2.5 | 763 | 4 | 0.5 | 0.0017 | 0.21 ( 0.07, | 0.62) | 0.21 ( 0.07, | 0.61) | -0.02 (-0.03,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.4091 |
| No | 629 | 14 | 2.2 | 589 | 3 | 0.5 | 0.0107 | 0.23 ( 0.07, | 0.79) | 0.22 ( 0.06, | 0.79) | -0.02 (-0.03, 0.00) | |
| Yes | 559 | 13 | 2.3 | 582 | 6 | 1.0 | 0.0876 | 0.44 ( 0.17, | 1.16) | 0.44 ( 0.17, | 1.16) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypokalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 22 | 1.9 | 1171 | 10 | 0.9 | 0.0362 | 0.46 ( 0.22, 0.97) | 0.46 ( 0.22, 0.97) | -0.01 (-0.02, 0.00) | | |
| Sex | | | | | | | | | | | | 0.4502 |
| Male | 864 | 15 | 1.7 | 837 | 8 | 1.0 | 0.1636 | 0.55 ( 0.23, 1.29) | 0.55 ( 0.23, 1.30) | -0.01 (-0.02, 0.00) | | |
| Female | 324 | 7 | 2.2 | 334 | 2 | 0.6 | 0.0847 | 0.28 ( 0.06, 1.32) | 0.27 ( 0.06, 1.32) | -0.02 (-0.03, 0.00) | | |
| Age [years] | | | | | | | | | | | | 0.6974 |
| <65 | 569 | 6 | 1.1 | 547 | 2 | 0.4 | 0.1727 | 0.35 ( 0.07, 1.71) | 0.34 ( 0.07, 1.71) | -0.01 (-0.02, 0.00) | | |
| >=65 | 619 | 16 | 2.6 | 624 | 8 | 1.3 | 0.0951 | 0.50 ( 0.21, 1.15) | 0.49 ( 0.21, 1.15) | -0.01 (-0.03, 0.00) | | |
| Region | | | | | | | | | | | | 0.9312 |
| Europe | 468 | 7 | 1.5 | 434 | 4 | 0.9 | 0.4325 | 0.62 ( 0.18, 2.09) | 0.61 ( 0.18, 2.11) | -0.01 (-0.02, 0.01) | | |
| North America | 259 | 7 | 2.7 | 241 | 3 | 1.2 | 0.2446 | 0.46 ( 0.12, 1.76) | 0.45 ( 0.12, 1.78) | -0.01 (-0.04, 0.01) | | |
| Latin America | 177 | 2 | 1.1 | 191 | 0 | 0 | 0.2202 | 0.19 (<0.01, 3.84) | 0.18 (<0.01, 3.84) | -0.01 (-0.03, 0.01) | | |
| Africa | 50 | 1 | 2.0 | 54 | 1 | 1.9 | 0.9562 | 0.93 ( 0.06, 14.41) | 0.92 ( 0.06, 15.19) | 0.00 (-0.05, 0.05) | | |
| Asia | 234 | 5 | 2.1 | 251 | 2 | 0.8 | 0.2163 | 0.37 ( 0.07, 1.90) | 0.37 ( 0.07, 1.91) | -0.01 (-0.03, 0.01) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7052 |
| <30 | 554 | 10 | 1.8 | 566 | 4 | 0.7 | 0.0981 | 0.39 ( 0.12, 1.24) | 0.39 ( 0.12, 1.24) | -0.01 (-0.02, 0.00) | | |
| >=30 | 634 | 12 | 1.9 | 605 | 6 | 1.0 | 0.1852 | 0.52 ( 0.20, 1.39) | 0.52 ( 0.19, 1.39) | -0.01 (-0.02, 0.00) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1012 |
| <130 | 379 | 9 | 2.4 | 382 | 1 | 0.3 | 0.0105 | 0.11 ( 0.01, 0.87) | 0.11 ( 0.01, 0.86) | -0.02 (-0.04, 0.00) | | |
| >=130 | 809 | 13 | 1.6 | 789 | 9 | 1.1 | 0.4239 | 0.71 ( 0.31, 1.65) | 0.71 ( 0.30, 1.66) | 0.00 (-0.02, 0.01) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3316 |
| <75 | 500 | 13 | 2.6 | 500 | 5 | 1.0 | 0.0571 | 0.38 ( 0.14, 1.07) | 0.38 ( 0.13, 1.07) | -0.02 (-0.03, 0.00) | | |
| 75 to <85 | 427 | 7 | 1.6 | 417 | 2 | 0.5 | 0.1010 | 0.29 ( 0.06, 1.40) | 0.29 ( 0.06, 1.40) | -0.01 (-0.03, 0.00) | | |
| >=85 | 261 | 2 | 0.8 | 254 | 3 | 1.2 | 0.6312 | 1.54 ( 0.26, 9.15) | 1.55 ( 0.26, 9.34) | 0.00 (-0.01, 0.02) | | |
| History of heart failure | | | | | | | | | | | | 0.9447 |
| No | 1048 | 20 | 1.9 | 1031 | 9 | 0.9 | 0.0441 | 0.46 ( 0.21, <1.00) | 0.45 ( 0.21, 1.00) | -0.01 (-0.02, 0.00) | | |
| Yes | 140 | 2 | 1.4 | 140 | 1 | 0.7 | 0.5616 | 0.50 ( 0.05, 5.45) | 0.50 ( 0.04, 5.54) | -0.01 (-0.03, 0.02) | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypokalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.3518 |
| <45 | 179 | 8 | 4.5 | 178 | 2 | 1.1 | 0.0554 | 0.25 ( 0.05, | 1.17) | 0.24 ( 0.05, | 1.16) | -0.03 (-0.07, 0.00) | |
| >=45 | 1009 | 14 | 1.4 | 993 | 8 | 0.8 | 0.2118 | 0.58 ( 0.24, | 1.38) | 0.58 ( 0.24, | 1.38) | -0.01 (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.5180 |
| Normal (<30) | 250 | 6 | 2.4 | 257 | 1 | 0.4 | 0.0524 | 0.16 ( 0.02, | 1.34) | 0.16 ( 0.02, | 1.33) | -0.02 (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 8 | 1.2 | 645 | 5 | 0.8 | 0.4508 | 0.65 ( 0.22, | 1.99) | 0.65 ( 0.21, | 2.00) | 0.00 (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 260 | 8 | 3.1 | 261 | 4 | 1.5 | 0.2400 | 0.50 ( 0.15, | 1.63) | 0.49 ( 0.15, | 1.65) | -0.02 (-0.04, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.5002 |
| Low, moderate or high | 1018 | 15 | 1.5 | 1001 | 8 | 0.8 | 0.1535 | 0.54 ( 0.23, | 1.27) | 0.54 ( 0.23, | 1.28) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 7 | 4.2 | 162 | 2 | 1.2 | 0.1002 | 0.29 ( 0.06, | 1.40) | 0.29 ( 0.06, | 1.40) | -0.03 (-0.06, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.6178 |
| No | 205 | 6 | 2.9 | 211 | 2 | 0.9 | 0.1417 | 0.32 ( 0.07, | 1.59) | 0.32 ( 0.06, | 1.59) | -0.02 (-0.05, 0.01) | |
| Yes | 983 | 16 | 1.6 | 960 | 8 | 0.8 | 0.1130 | 0.51 ( 0.22, | 1.19) | 0.51 ( 0.22, | 1.19) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.8450 |
| No | 422 | 6 | 1.4 | 408 | 3 | 0.7 | 0.3397 | 0.52 ( 0.13, | 2.05) | 0.51 ( 0.13, | 2.07) | -0.01 (-0.02, 0.01) | |
| Yes | 766 | 16 | 2.1 | 763 | 7 | 0.9 | 0.0599 | 0.44 ( 0.18, | 1.06) | 0.43 ( 0.18, | 1.06) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.6450 |
| No | 629 | 9 | 1.4 | 589 | 3 | 0.5 | 0.1037 | 0.36 ( 0.10, | 1.31) | 0.35 ( 0.10, | 1.31) | -0.01 (-0.02, 0.00) | |
| Yes | 559 | 13 | 2.3 | 582 | 7 | 1.2 | 0.1485 | 0.52 ( 0.21, | 1.29) | 0.51 ( 0.20, | 1.29) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Dehydration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 19 | 1.6 | 0.2674 | 1.48 ( 0.74, 2.99) | 1.49 ( 0.73, 3.03) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Decreased appetite

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 16 | 1.3 | 1171 | 11 | 0.9 | 0.3523 | 0.70 ( 0.33, 1.50) | 0.69 ( 0.32, 1.50) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Vitamin D deficiency

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 7 | 0.6 | 1171 | 14 | 1.2 | 0.1170 | 2.03 ( 0.82, 5.01) | 2.04 ( 0.82, 5.08) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperlipidaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 10 | 0.9 | 0.6932 | 0.85 ( 0.37, | 1.95) | 0.84 ( 0.36, | 1.96) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Diarrhoea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 110 | 9.3 | 1171 | 88 | 7.5 | 0.1266 | 0.81 ( 0.62, 1.06) | 0.80 ( 0.59, 1.07) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Constipation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 79 | 6.6 | 1171 | 51 | 4.4 | 0.0146 | 0.65 | ( 0.46, 0.92) | 0.64 | ( 0.45, 0.92) | -0.02 | (-0.04, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.6027 |
| Male | 864 | 57 | 6.6 | 837 | 34 | 4.1 | 0.0202 | 0.62 | ( 0.41, 0.93) | 0.60 | ( 0.39, 0.93) | -0.03 | (-0.05, 0.00) | |
| Female | 324 | 22 | 6.8 | 334 | 17 | 5.1 | 0.3558 | 0.75 | ( 0.41, 1.39) | 0.74 | ( 0.38, 1.41) | -0.02 | (-0.05, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.3696 |
| <65 | 569 | 30 | 5.3 | 547 | 15 | 2.7 | 0.0317 | 0.52 | ( 0.28, 0.96) | 0.51 | ( 0.27, 0.95) | -0.03 | (-0.05, 0.00) | |
| >=65 | 619 | 49 | 7.9 | 624 | 36 | 5.8 | 0.1338 | 0.73 | ( 0.48, 1.10) | 0.71 | ( 0.46, 1.11) | -0.02 | (-0.05, 0.01) | |
| Region | | | | | | | | | | | | | | 0.1651 |
| Europe | 468 | 28 | 6.0 | 434 | 10 | 2.3 | 0.0060 | 0.39 | ( 0.19, 0.78) | 0.37 | ( 0.18, 0.77) | -0.04 | (-0.06,-0.01) | |
| North America | 259 | 23 | 8.9 | 241 | 10 | 4.1 | 0.0333 | 0.47 | ( 0.23, 0.96) | 0.44 | ( 0.21, 0.95) | -0.05 | (-0.09, 0.00) | |
| Latin America | 177 | 9 | 5.1 | 191 | 10 | 5.2 | 0.9479 | 1.03 | ( 0.43, 2.48) | 1.03 | ( 0.41, 2.60) | 0.00 | (-0.04, 0.05) | |
| Africa | 50 | 5 | 10.0 | 54 | 4 | 7.4 | 0.6385 | 0.74 | ( 0.21, 2.60) | 0.72 | ( 0.18, 2.85) | -0.03 | (-0.13, 0.08) | |
| Asia | 234 | 14 | 6.0 | 251 | 17 | 6.8 | 0.7223 | 1.13 | ( 0.57, 2.24) | 1.14 | ( 0.55, 2.37) | 0.01 | (-0.04, 0.05) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7200 |
| <30 | 554 | 38 | 6.9 | 566 | 27 | 4.8 | 0.1349 | 0.70 | ( 0.43, 1.12) | 0.68 | ( 0.41, 1.13) | -0.02 | (-0.05, 0.01) | |
| >=30 | 634 | 41 | 6.5 | 605 | 24 | 4.0 | 0.0485 | 0.61 | ( 0.38, >1.00) | 0.60 | ( 0.36, 1.00) | -0.02 | (-0.05, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5774 |
| <130 | 379 | 31 | 8.2 | 382 | 18 | 4.7 | 0.0514 | 0.58 | ( 0.33, 1.01) | 0.56 | ( 0.30, 1.01) | -0.03 | (-0.07, 0.00) | |
| >=130 | 809 | 48 | 5.9 | 789 | 33 | 4.2 | 0.1107 | 0.70 | ( 0.46, 1.09) | 0.69 | ( 0.44, 1.09) | -0.02 | (-0.04, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9613 |
| <75 | 500 | 40 | 8.0 | 500 | 25 | 5.0 | 0.0543 | 0.63 | ( 0.39, 1.01) | 0.61 | ( 0.36, 1.01) | -0.03 | (-0.06, 0.00) | |
| 75 to <85 | 427 | 26 | 6.1 | 417 | 17 | 4.1 | 0.1838 | 0.67 | ( 0.37, 1.22) | 0.66 | ( 0.35, 1.23) | -0.02 | (-0.05, 0.01) | |
| >=85 | 261 | 13 | 5.0 | 254 | 9 | 3.5 | 0.4199 | 0.71 | ( 0.31, 1.63) | 0.70 | ( 0.29, 1.67) | -0.01 | (-0.05, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.2504 |
| No | 1048 | 64 | 6.1 | 1031 | 45 | 4.4 | 0.0748 | 0.71 | ( 0.49, 1.04) | 0.70 | ( 0.47, 1.04) | -0.02 | (-0.04, 0.00) | |
| Yes | 140 | 15 | 10.7 | 140 | 6 | 4.3 | 0.0411 | 0.40 | ( 0.16, >1.00) | 0.37 | ( 0.14, 0.99) | -0.06 | (-0.13, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Constipation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.9233 |
| <45 | 179 | 19 | 10.6 | 178 | 12 | 6.7 | 0.1938 | 0.64 ( 0.32, | 1.27) | 0.61 ( 0.29, | 1.29) | -0.04 (-0.10, 0.02) | |
| >=45 | 1009 | 60 | 5.9 | 993 | 39 | 3.9 | 0.0372 | 0.66 ( 0.45, | 0.98) | 0.65 ( 0.43, | 0.98) | -0.02 (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.3720 |
| Normal (<30) | 250 | 23 | 9.2 | 257 | 14 | 5.4 | 0.1044 | 0.59 ( 0.31, | 1.12) | 0.57 ( 0.29, | 1.13) | -0.04 (-0.08, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 34 | 5.0 | 645 | 27 | 4.2 | 0.4616 | 0.83 ( 0.51, | 1.36) | 0.82 ( 0.49, | 1.38) | -0.01 (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 260 | 22 | 8.5 | 261 | 10 | 3.8 | 0.0277 | 0.45 ( 0.22, | 0.94) | 0.43 ( 0.20, | 0.93) | -0.05 (-0.09,-0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.4852 |
| Low, moderate or high | 1018 | 61 | 6.0 | 1001 | 42 | 4.2 | 0.0666 | 0.70 ( 0.48, | 1.03) | 0.69 ( 0.46, | 1.03) | -0.02 (-0.04, 0.00) | |
| Very high | 167 | 18 | 10.8 | 162 | 9 | 5.6 | 0.0844 | 0.52 ( 0.24, | 1.11) | 0.49 ( 0.21, | 1.12) | -0.05 (-0.11, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.5890 |
| No | 205 | 8 | 3.9 | 211 | 7 | 3.3 | 0.7490 | 0.85 ( 0.31, | 2.30) | 0.84 ( 0.30, | 2.37) | -0.01 (-0.04, 0.03) | |
| Yes | 983 | 71 | 7.2 | 960 | 44 | 4.6 | 0.0137 | 0.63 ( 0.44, | 0.91) | 0.62 ( 0.42, | 0.91) | -0.03 (-0.05,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.4034 |
| No | 422 | 26 | 6.2 | 408 | 20 | 4.9 | 0.4280 | 0.80 ( 0.45, | 1.40) | 0.79 ( 0.43, | 1.43) | -0.01 (-0.04, 0.02) | |
| Yes | 766 | 53 | 6.9 | 763 | 31 | 4.1 | 0.0143 | 0.59 ( 0.38, | 0.90) | 0.57 ( 0.36, | 0.90) | -0.03 (-0.05,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.5363 |
| No | 629 | 35 | 5.6 | 589 | 24 | 4.1 | 0.2262 | 0.73 ( 0.44, | 1.22) | 0.72 ( 0.42, | 1.23) | -0.01 (-0.04, 0.01) | |
| Yes | 559 | 44 | 7.9 | 582 | 27 | 4.6 | 0.0239 | 0.59 ( 0.37, | 0.94) | 0.57 ( 0.35, | 0.93) | -0.03 (-0.06, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Nausea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 48 | 4.0 | 1171 | 49 | 4.2 | 0.8602 | 1.04 ( 0.70, 1.53) | 1.04 ( 0.69, 1.56) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Vomiting

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 44 | 3.7 | 1171 | 42 | 3.6 | 0.8795 | 0.97 ( 0.64, 1.47) | 0.97 ( 0.63, 1.49) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Abdominal pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 32 | 2.7 | 1171 | 37 | 3.2 | 0.5018 | 1.17 ( 0.74, 1.87) | 1.18 ( 0.73, 1.91) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Dyspepsia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 36 | 3.0 | 1171 | 18 | 1.5 | 0.0153 | 0.51 ( 0.29, | 0.89) | 0.50 ( 0.28, | 0.88) | -0.01 (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | 0.4643 |
| Male | 864 | 26 | 3.0 | 837 | 11 | 1.3 | 0.0166 | 0.44 ( 0.22, | 0.88) | 0.43 ( 0.21, | 0.87) | -0.02 (-0.03, 0.00) | |
| Female | 324 | 10 | 3.1 | 334 | 7 | 2.1 | 0.4233 | 0.68 ( 0.26, | 1.76) | 0.67 ( 0.25, | 1.79) | -0.01 (-0.03, 0.01) | |
| Age [years] | | | | | | | | | | | | | 0.6142 |
| <65 | 569 | 17 | 3.0 | 547 | 7 | 1.3 | 0.0493 | 0.43 ( 0.18, | 1.02) | 0.42 ( 0.17, | 1.02) | -0.02 (-0.03, 0.00) | |
| >=65 | 619 | 19 | 3.1 | 624 | 11 | 1.8 | 0.1334 | 0.57 ( 0.28, | 1.20) | 0.57 ( 0.27, | 1.20) | -0.01 (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | 0.9294 |
| Europe | 468 | 8 | 1.7 | 434 | 4 | 0.9 | 0.3022 | 0.54 ( 0.16, | 1.78) | 0.53 ( 0.16, | 1.79) | -0.01 (-0.02, 0.01) | |
| North America | 259 | 4 | 1.5 | 241 | 1 | 0.4 | 0.2047 | 0.27 ( 0.03, | 2.39) | 0.27 ( 0.03, | 2.39) | -0.01 (-0.03, 0.01) | |
| Latin America | 177 | 6 | 3.4 | 191 | 4 | 2.1 | 0.4450 | 0.62 ( 0.18, | 2.15) | 0.61 ( 0.17, | 2.20) | -0.01 (-0.05, 0.02) | |
| Africa | 50 | 2 | 4.0 | 54 | 0 | 0 | 0.2155 | 0.19 (<0.01, | 3.77) | 0.18 (<0.01, | 3.80) | -0.04 (-0.10, 0.02) | |
| Asia | 234 | 16 | 6.8 | 251 | 9 | 3.6 | 0.1056 | 0.52 ( 0.24, | 1.16) | 0.51 ( 0.22, | 1.17) | -0.03 (-0.07, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.9355 |
| <30 | 554 | 21 | 3.8 | 566 | 11 | 1.9 | 0.0636 | 0.51 ( 0.25, | 1.05) | 0.50 ( 0.24, | 1.05) | -0.02 (-0.04, 0.00) | |
| >=30 | 634 | 15 | 2.4 | 605 | 7 | 1.2 | 0.1073 | 0.49 ( 0.20, | 1.19) | 0.48 ( 0.20, | 1.19) | -0.01 (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.5218 |
| <130 | 379 | 19 | 5.0 | 382 | 8 | 2.1 | 0.0295 | 0.42 ( 0.19, | 0.94) | 0.41 ( 0.18, | 0.94) | -0.03 (-0.06, 0.00) | |
| >=130 | 809 | 17 | 2.1 | 789 | 10 | 1.3 | 0.1959 | 0.60 ( 0.28, | 1.31) | 0.60 ( 0.27, | 1.31) | -0.01 (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.8986 |
| <75 | 500 | 19 | 3.8 | 500 | 9 | 1.8 | 0.0553 | 0.47 ( 0.22, | 1.04) | 0.46 ( 0.21, | 1.04) | -0.02 (-0.04, 0.00) | |
| 75 to <85 | 427 | 12 | 2.8 | 417 | 7 | 1.7 | 0.2678 | 0.60 ( 0.24, | 1.50) | 0.59 ( 0.23, | 1.51) | -0.01 (-0.03, 0.01) | |
| >=85 | 261 | 5 | 1.9 | 254 | 2 | 0.8 | 0.2689 | 0.41 ( 0.08, | 2.10) | 0.41 ( 0.08, | 2.11) | -0.01 (-0.03, 0.01) | |
| History of heart failure | | | | | | | | | | | | | 0.5287 |
| No | 1048 | 34 | 3.2 | 1031 | 18 | 1.7 | 0.0287 | 0.54 ( 0.31, | 0.95) | 0.53 ( 0.30, | 0.94) | -0.01 (-0.03, 0.00) | |
| Yes | 140 | 2 | 1.4 | 140 | 0 | 0 | 0.2457 | 0.20 (<0.01, | 4.13) | 0.20 (<0.01, | 4.14) | -0.01 (-0.04, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Dyspepsia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2228 |
| <45 | 179 | 5 | 2.8 | 178 | 5 | 2.8 | 0.9928 | 1.01 ( 0.30, 3.41) | 1.01 ( 0.29, 3.54) | 0.00 | (-0.03, 0.03) | |
| >=45 | 1009 | 31 | 3.1 | 993 | 13 | 1.3 | 0.0071 | 0.43 ( 0.22, 0.81) | 0.42 ( 0.22, 0.80) | -0.02 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7666 |
| Normal (<30) | 250 | 6 | 2.4 | 257 | 4 | 1.6 | 0.4946 | 0.65 ( 0.19, 2.27) | 0.64 ( 0.18, 2.31) | -0.01 | (-0.03, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 19 | 2.8 | 645 | 10 | 1.6 | 0.1172 | 0.55 ( 0.26, 1.18) | 0.54 ( 0.25, 1.18) | -0.01 | (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 260 | 11 | 4.2 | 261 | 4 | 1.5 | 0.0655 | 0.36 ( 0.12, 1.12) | 0.35 ( 0.11, 1.12) | -0.03 | (-0.06, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0336 |
| Low, moderate or high | 1018 | 34 | 3.3 | 1001 | 13 | 1.3 | 0.0024 | 0.39 ( 0.21, 0.73) | 0.38 ( 0.20, 0.73) | -0.02 | (-0.03,-0.01) | |
| Very high | 167 | 2 | 1.2 | 162 | 5 | 3.1 | 0.2353 | 2.58 ( 0.51, 13.09) | 2.63 ( 0.50, 13.74) | 0.02 | (-0.01, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.3779 |
| No | 205 | 6 | 2.9 | 211 | 5 | 2.4 | 0.7233 | 0.81 ( 0.25, 2.61) | 0.81 ( 0.24, 2.68) | -0.01 | (-0.04, 0.03) | |
| Yes | 983 | 30 | 3.1 | 960 | 13 | 1.4 | 0.0110 | 0.44 ( 0.23, 0.85) | 0.44 ( 0.23, 0.84) | -0.02 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6909 |
| No | 422 | 10 | 2.4 | 408 | 4 | 1.0 | 0.1202 | 0.41 ( 0.13, 1.31) | 0.41 ( 0.13, 1.31) | -0.01 | (-0.03, 0.00) | |
| Yes | 766 | 26 | 3.4 | 763 | 14 | 1.8 | 0.0561 | 0.54 ( 0.28, 1.03) | 0.53 ( 0.28, 1.03) | -0.02 | (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3372 |
| No | 629 | 18 | 2.9 | 589 | 11 | 1.9 | 0.2554 | 0.65 ( 0.31, 1.37) | 0.65 ( 0.30, 1.38) | -0.01 | (-0.03, 0.01) | |
| Yes | 559 | 18 | 3.2 | 582 | 7 | 1.2 | 0.0200 | 0.37 ( 0.16, 0.89) | 0.37 ( 0.15, 0.88) | -0.02 | (-0.04, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Gastritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 29 | 2.4 | 1171 | 32 | 2.7 | 0.6554 | 1.12 ( 0.68, 1.84) | 1.12 ( 0.67, 1.87) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Abdominal pain upper

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 28 | 2.4 | 1171 | 19 | 1.6 | 0.2019 | 0.69 ( 0.39, 1.23) | 0.68 ( 0.38, 1.23) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Gastrooesophageal reflux disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 28 | 2.4 | 1171 | 25 | 2.1 | 0.7161 | 0.91 ( 0.53, 1.54) | 0.90 ( 0.52, 1.56) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Abdominal distension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 17 | 1.4 | 1171 | 8 | 0.7 | 0.0762 | 0.48 ( 0.21, 1.10) | 0.47 ( 0.20, 1.10) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Dry mouth

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 7 | 0.6 | 1171 | 16 | 1.4 | 0.0548 | 2.32 ( 0.96, 5.62) | 2.34 ( 0.96, 5.70) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Large intestine polyp

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 15 | 1.3 | 0.9683 | 1.01 ( 0.50, 2.07) | 1.01 ( 0.49, 2.09) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Toothache

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 11 | 0.9 | 1171 | 15 | 1.3 | 0.4089 | 1.38 ( 0.64, 3.00) | 1.39 ( 0.64, 3.04) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Haemorrhoids

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 13 | 1.1 | 0.7324 | 0.88 ( 0.42, 1.84) | 0.88 ( 0.42, 1.85) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina unstable

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 53 | 4.5 | 1171 | 42 | 3.6 | 0.2800 | 0.80 ( 0.54, 1.20) | 0.80 ( 0.53, 1.20) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 50 | 4.2 | 1171 | 34 | 2.9 | 0.0872 | 0.69 ( 0.45, 1.06) | 0.68 ( 0.44, 1.06) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 40 | 3.4 | 1171 | 46 | 3.9 | 0.4671 | 1.17 ( 0.77, 1.77) | 1.17 ( 0.76, 1.81) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina pectoris

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 43 | 3.6 | 1171 | 42 | 3.6 | 0.9659 | 0.99 ( 0.65, 1.50) | 0.99 ( 0.64, 1.53) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 43 | 3.6 | 1171 | 23 | 2.0 | 0.0148 | 0.54 | ( 0.33, 0.89) | 0.53 | ( 0.32, 0.89) | -0.02 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0561 |
| Male | 864 | 26 | 3.0 | 837 | 19 | 2.3 | 0.3422 | 0.75 | ( 0.42, 1.35) | 0.75 | ( 0.41, 1.36) | -0.01 | (-0.02, 0.01) | |
| Female | 324 | 17 | 5.2 | 334 | 4 | 1.2 | 0.0031 | 0.23 | ( 0.08, 0.67) | 0.22 | ( 0.07, 0.66) | -0.04 | (-0.07,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.0347 |
| <65 | 569 | 15 | 2.6 | 547 | 14 | 2.6 | 0.9358 | 0.97 | ( 0.47, 1.99) | 0.97 | ( 0.46, 2.03) | 0.00 | (-0.02, 0.02) | |
| >=65 | 619 | 28 | 4.5 | 624 | 9 | 1.4 | 0.0014 | 0.32 | ( 0.15, 0.67) | 0.31 | ( 0.14, 0.66) | -0.03 | (-0.05,-0.01) | |
| Region | | | | | | | | | | | | | | 0.4493 |
| Europe | 468 | 8 | 1.7 | 434 | 6 | 1.4 | 0.6915 | 0.81 | ( 0.28, 2.31) | 0.81 | ( 0.28, 2.34) | 0.00 | (-0.02, 0.01) | |
| North America | 259 | 20 | 7.7 | 241 | 6 | 2.5 | 0.0085 | 0.32 | ( 0.13, 0.79) | 0.31 | ( 0.12, 0.77) | -0.05 | (-0.09,-0.01) | |
| Latin America | 177 | 5 | 2.8 | 191 | 2 | 1.0 | 0.2123 | 0.37 | ( 0.07, 1.89) | 0.36 | ( 0.07, 1.90) | -0.02 | (-0.05, 0.01) | |
| Africa | 50 | 4 | 8.0 | 54 | 2 | 3.7 | 0.3478 | 0.46 | ( 0.09, 2.42) | 0.44 | ( 0.08, 2.53) | -0.04 | (-0.13, 0.05) | |
| Asia | 234 | 6 | 2.6 | 251 | 7 | 2.8 | 0.8783 | 1.09 | ( 0.37, 3.19) | 1.09 | ( 0.36, 3.29) | 0.00 | (-0.03, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4867 |
| <30 | 554 | 18 | 3.2 | 566 | 8 | 1.4 | 0.0414 | 0.44 | ( 0.19, 0.99) | 0.43 | ( 0.18, 0.99) | -0.02 | (-0.04, 0.00) | |
| >=30 | 634 | 25 | 3.9 | 605 | 15 | 2.5 | 0.1451 | 0.63 | ( 0.33, 1.18) | 0.62 | ( 0.32, 1.19) | -0.01 | (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5178 |
| <130 | 379 | 20 | 5.3 | 382 | 9 | 2.4 | 0.0353 | 0.45 | ( 0.21, 0.97) | 0.43 | ( 0.19, 0.96) | -0.03 | (-0.06, 0.00) | |
| >=130 | 809 | 23 | 2.8 | 789 | 14 | 1.8 | 0.1556 | 0.62 | ( 0.32, 1.20) | 0.62 | ( 0.32, 1.21) | -0.01 | (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9852 |
| <75 | 500 | 23 | 4.6 | 500 | 12 | 2.4 | 0.0584 | 0.52 | ( 0.26, 1.04) | 0.51 | ( 0.25, 1.04) | -0.02 | (-0.04, 0.00) | |
| 75 to <85 | 427 | 13 | 3.0 | 417 | 7 | 1.7 | 0.1921 | 0.55 | ( 0.22, 1.37) | 0.54 | ( 0.21, 1.38) | -0.01 | (-0.03, 0.01) | |
| >=85 | 261 | 7 | 2.7 | 254 | 4 | 1.6 | 0.3849 | 0.59 | ( 0.17, 1.98) | 0.58 | ( 0.17, 2.01) | -0.01 | (-0.04, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.2239 |
| No | 1048 | 29 | 2.8 | 1031 | 12 | 1.2 | 0.0086 | 0.42 | ( 0.22, 0.82) | 0.41 | ( 0.21, 0.82) | -0.02 | (-0.03, 0.00) | |
| Yes | 140 | 14 | 10.0 | 140 | 11 | 7.9 | 0.5295 | 0.79 | ( 0.37, 1.67) | 0.77 | ( 0.34, 1.75) | -0.02 | (-0.09, 0.05) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.0412 |
| <45 | 179 | 14 | 7.8 | 178 | 2 | 1.1 | 0.0022 | 0.14 ( 0.03, | 0.62) | 0.13 ( 0.03, | 0.60) | -0.07 (-0.11,-0.02) | |
| >=45 | 1009 | 29 | 2.9 | 993 | 21 | 2.1 | 0.2763 | 0.74 ( 0.42, | 1.28) | 0.73 ( 0.41, | 1.29) | -0.01 (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.7896 |
| Normal (<30) | 250 | 8 | 3.2 | 257 | 4 | 1.6 | 0.2236 | 0.49 ( 0.15, | 1.59) | 0.48 ( 0.14, | 1.61) | -0.02 (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 22 | 3.3 | 645 | 10 | 1.6 | 0.0436 | 0.48 ( 0.23, | <1.00) | 0.47 ( 0.22, | 0.99) | -0.02 (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 260 | 13 | 5.0 | 261 | 9 | 3.4 | 0.3785 | 0.69 ( 0.30, | 1.59) | 0.68 ( 0.28, | 1.62) | -0.02 (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.2726 |
| Low, moderate or high | 1018 | 28 | 2.8 | 1001 | 18 | 1.8 | 0.1516 | 0.65 ( 0.36, | 1.17) | 0.65 ( 0.36, | 1.18) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 15 | 9.0 | 162 | 5 | 3.1 | 0.0253 | 0.34 ( 0.13, | 0.92) | 0.32 ( 0.11, | 0.91) | -0.06 (-0.11,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.3859 |
| No | 205 | 9 | 4.4 | 211 | 3 | 1.4 | 0.0705 | 0.32 ( 0.09, | 1.18) | 0.31 ( 0.08, | 1.18) | -0.03 (-0.06, 0.00) | |
| Yes | 983 | 34 | 3.5 | 960 | 20 | 2.1 | 0.0652 | 0.60 ( 0.35, | 1.04) | 0.59 ( 0.34, | 1.04) | -0.01 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.6082 |
| No | 422 | 10 | 2.4 | 408 | 4 | 1.0 | 0.1202 | 0.41 ( 0.13, | 1.31) | 0.41 ( 0.13, | 1.31) | -0.01 (-0.03, 0.00) | |
| Yes | 766 | 33 | 4.3 | 763 | 19 | 2.5 | 0.0499 | 0.58 ( 0.33, | 1.01) | 0.57 ( 0.32, | 1.01) | -0.02 (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.6925 |
| No | 629 | 10 | 1.6 | 589 | 4 | 0.7 | 0.1362 | 0.43 ( 0.13, | 1.35) | 0.42 ( 0.13, | 1.36) | -0.01 (-0.02, 0.00) | |
| Yes | 559 | 33 | 5.9 | 582 | 19 | 3.3 | 0.0326 | 0.55 ( 0.32, | 0.96) | 0.54 ( 0.30, | 0.96) | -0.03 (-0.05, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 38 | 3.2 | 1171 | 34 | 2.9 | 0.6769 | 0.91 ( 0.58, 1.43) | 0.90 ( 0.57, 1.45) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Coronary artery disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 34 | 2.9 | 1171 | 19 | 1.6 | 0.0423 | 0.57 | ( 0.33, 0.99) | 0.56 | ( 0.32, 0.99) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.7643 |
| Male | 864 | 25 | 2.9 | 837 | 13 | 1.6 | 0.0615 | 0.54 | ( 0.28, 1.04) | 0.53 | ( 0.27, 1.04) | -0.01 | (-0.03, 0.00) | |
| Female | 324 | 9 | 2.8 | 334 | 6 | 1.8 | 0.3991 | 0.65 | ( 0.23, 1.80) | 0.64 | ( 0.23, 1.82) | -0.01 | (-0.03, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.7888 |
| <65 | 569 | 16 | 2.8 | 547 | 8 | 1.5 | 0.1203 | 0.52 | ( 0.22, 1.21) | 0.51 | ( 0.22, 1.21) | -0.01 | (-0.03, 0.00) | |
| >=65 | 619 | 18 | 2.9 | 624 | 11 | 1.8 | 0.1811 | 0.61 | ( 0.29, 1.27) | 0.60 | ( 0.28, 1.28) | -0.01 | (-0.03, 0.01) | |
| Region | | | | | | | | | | | | | | 0.9780 |
| Europe | 468 | 11 | 2.4 | 434 | 6 | 1.4 | 0.2855 | 0.59 | ( 0.22, 1.58) | 0.58 | ( 0.21, 1.59) | -0.01 | (-0.03, 0.01) | |
| North America | 259 | 12 | 4.6 | 241 | 5 | 2.1 | 0.1147 | 0.45 | ( 0.16, 1.25) | 0.44 | ( 0.15, 1.26) | -0.03 | (-0.06, 0.01) | |
| Latin America | 177 | 6 | 3.4 | 191 | 4 | 2.1 | 0.4450 | 0.62 | ( 0.18, 2.15) | 0.61 | ( 0.17, 2.20) | -0.01 | (-0.05, 0.02) | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | 0.9697 | 0.93 | ( 0.02, 45.87) | 0.93 | ( 0.02, 47.58) | 0.00 | (-0.04, 0.04) | |
| Asia | 234 | 5 | 2.1 | 251 | 4 | 1.6 | 0.6578 | 0.75 | ( 0.20, 2.74) | 0.74 | ( 0.20, 2.80) | -0.01 | (-0.03, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4180 |
| <30 | 554 | 14 | 2.5 | 566 | 6 | 1.1 | 0.0638 | 0.42 | ( 0.16, 1.08) | 0.41 | ( 0.16, 1.08) | -0.01 | (-0.03, 0.00) | |
| >=30 | 634 | 20 | 3.2 | 605 | 13 | 2.1 | 0.2717 | 0.68 | ( 0.34, 1.36) | 0.67 | ( 0.33, 1.37) | -0.01 | (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3540 |
| <130 | 379 | 11 | 2.9 | 382 | 4 | 1.0 | 0.0656 | 0.36 | ( 0.12, 1.12) | 0.35 | ( 0.11, 1.12) | -0.02 | (-0.04, 0.00) | |
| >=130 | 809 | 23 | 2.8 | 789 | 15 | 1.9 | 0.2166 | 0.67 | ( 0.35, 1.27) | 0.66 | ( 0.34, 1.28) | -0.01 | (-0.02, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0197 |
| <75 | 500 | 18 | 3.6 | 500 | 7 | 1.4 | 0.0259 | 0.39 | ( 0.16, 0.92) | 0.38 | ( 0.16, 0.92) | -0.02 | (-0.04, 0.00) | |
| 75 to <85 | 427 | 12 | 2.8 | 417 | 3 | 0.7 | 0.0215 | 0.26 | ( 0.07, 0.90) | 0.25 | ( 0.07, 0.89) | -0.02 | (-0.04, 0.00) | |
| >=85 | 261 | 4 | 1.5 | 254 | 9 | 3.5 | 0.1458 | 2.31 | ( 0.72, 7.41) | 2.36 | ( 0.72, 7.76) | 0.02 | (-0.01, 0.05) | |
| History of heart failure | | | | | | | | | | | | | | 0.1586 |
| No | 1048 | 27 | 2.6 | 1031 | 18 | 1.7 | 0.1933 | 0.68 | ( 0.38, 1.22) | 0.67 | ( 0.37, 1.23) | -0.01 | (-0.02, 0.00) | |
| Yes | 140 | 7 | 5.0 | 140 | 1 | 0.7 | 0.0314 | 0.14 | ( 0.02, 1.15) | 0.14 | ( 0.02, 1.13) | -0.04 | (-0.08, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Coronary artery disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4417 |
| <45 | 179 | 4 | 2.2 | 178 | 1 | 0.6 | 0.1787 | 0.25 ( 0.03, 2.23) | 0.25 ( 0.03, 2.23) | -0.02 | (-0.04, 0.01) | |
| >=45 | 1009 | 30 | 3.0 | 993 | 18 | 1.8 | 0.0897 | 0.61 ( 0.34, 1.09) | 0.60 ( 0.33, 1.09) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7783 |
| Normal (<30) | 250 | 8 | 3.2 | 257 | 5 | 1.9 | 0.3716 | 0.61 ( 0.20, 1.83) | 0.60 ( 0.19, 1.86) | -0.01 | (-0.04, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 18 | 2.7 | 645 | 11 | 1.7 | 0.2337 | 0.64 ( 0.30, 1.34) | 0.63 ( 0.30, 1.35) | -0.01 | (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 260 | 8 | 3.1 | 261 | 3 | 1.1 | 0.1260 | 0.37 ( 0.10, 1.39) | 0.37 ( 0.10, 1.40) | -0.02 | (-0.04, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5334 |
| Low, moderate or high | 1018 | 32 | 3.1 | 1001 | 17 | 1.7 | 0.0349 | 0.54 ( 0.30, 0.97) | 0.53 ( 0.29, 0.96) | -0.01 | (-0.03, 0.00) | |
| Very high | 167 | 2 | 1.2 | 162 | 2 | 1.2 | 0.9756 | 1.03 ( 0.15, 7.23) | 1.03 ( 0.14, 7.41) | 0.00 | (-0.02, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.1367 |
| No | 205 | 1 | 0.5 | 211 | 3 | 1.4 | 0.3291 | 2.91 ( 0.31, 27.79) | 2.94 ( 0.30, 28.52) | 0.01 | (-0.01, 0.03) | |
| Yes | 983 | 33 | 3.4 | 960 | 16 | 1.7 | 0.0175 | 0.50 ( 0.28, 0.90) | 0.49 ( 0.27, 0.89) | -0.02 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9169 |
| No | 422 | 4 | 0.9 | 408 | 2 | 0.5 | 0.4365 | 0.52 ( 0.10, 2.81) | 0.51 ( 0.09, 2.83) | 0.00 | (-0.02, 0.01) | |
| Yes | 766 | 30 | 3.9 | 763 | 17 | 2.2 | 0.0558 | 0.57 ( 0.32, 1.02) | 0.56 ( 0.31, 1.02) | -0.02 | (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | 0.1349 |
| No | 629 | 15 | 2.4 | 589 | 4 | 0.7 | 0.0164 | 0.28 ( 0.10, 0.85) | 0.28 ( 0.09, 0.85) | -0.02 | (-0.03, 0.00) | |
| Yes | 559 | 19 | 3.4 | 582 | 15 | 2.6 | 0.4145 | 0.76 ( 0.39, 1.48) | 0.75 ( 0.38, 1.49) | -0.01 | (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 31 | 2.6 | 1171 | 22 | 1.9 | 0.2312 | 0.72 ( 0.42, 1.24) | 0.71 ( 0.41, 1.24) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Palpitations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** | |
| Overall | 1188 | 18 | 1.5 | 1171 | 10 | 0.9 | 0.1382 | 0.56 ( 0.26, 1.22) | 0.56 ( 0.26, 1.22) | -0.01 (-0.02, 0.00) | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Bradycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 8 | 0.7 | 0.2108 | 0.58 ( 0.24, 1.38) | 0.58 ( 0.24, 1.38) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Tachycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 6 | 0.5 | 0.0777 | 0.43 ( 0.17, 1.13) | 0.43 ( 0.17, 1.13) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular extrasystoles

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 13 | 1.1 | 0.9705 | 1.01 ( 0.47, 2.18) | 1.01 ( 0.47, 2.20) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Bundle branch block left

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 3 | 0.3 | 0.0132 | 0.23 ( 0.07, 0.82) | 0.23 ( 0.07, 0.82) | -0.01 (-0.01, 0.00) | | |
| Sex | | | | | | | | | | | | 0.8245 |
| Male | 864 | 11 | 1.3 | 837 | 3 | 0.4 | 0.0368 | 0.28 ( 0.08, 1.01) | 0.28 ( 0.08, 1.00) | -0.01 (-0.02, 0.00) | | |
| Female | 324 | 2 | 0.6 | 334 | 0 | 0 | 0.2365 | 0.19 (<0.01, 4.03) | 0.19 (<0.01, 4.03) | -0.01 (-0.02, 0.00) | | |
| Age [years] | | | | | | | | | | | | 0.6875 |
| <65 | 569 | 3 | 0.5 | 547 | 1 | 0.2 | 0.3358 | 0.35 ( 0.04, 3.32) | 0.35 ( 0.04, 3.33) | 0.00 (-0.01, 0.00) | | |
| >=65 | 619 | 10 | 1.6 | 624 | 2 | 0.3 | 0.0196 | 0.20 ( 0.04, 0.90) | 0.20 ( 0.04, 0.90) | -0.01 (-0.02, 0.00) | | |
| Region | | | | | | | | | | | | |
| Europe | 468 | 3 | 0.6 | 434 | 1 | 0.2 | | | | | | |
| North America | 259 | 2 | 0.8 | 241 | 0 | 0 | | | | | | |
| Latin America | 177 | 5 | 2.8 | 191 | 2 | 1.0 | | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | | |
| Asia | 234 | 3 | 1.3 | 251 | 0 | 0 | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.4545 |
| <30 | 554 | 11 | 2.0 | 566 | 2 | 0.4 | 0.0108 | 0.18 ( 0.04, 0.80) | 0.18 ( 0.04, 0.79) | -0.02 (-0.03, 0.00) | | |
| >=30 | 634 | 2 | 0.3 | 605 | 1 | 0.2 | 0.5908 | 0.52 ( 0.05, 5.76) | 0.52 ( 0.05, 5.78) | 0.00 (-0.01, 0.00) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 379 | 8 | 2.1 | 382 | 0 | 0 | | | | | | |
| >=130 | 809 | 5 | 0.6 | 789 | 3 | 0.4 | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 500 | 6 | 1.2 | 500 | 1 | 0.2 | | | | | | |
| 75 to <85 | 427 | 6 | 1.4 | 417 | 1 | 0.2 | | | | | | |
| >=85 | 261 | 1 | 0.4 | 254 | 1 | 0.4 | | | | | | |
| History of heart failure | | | | | | | | | | | | 0.4891 |
| No | 1048 | 13 | 1.2 | 1031 | 3 | 0.3 | 0.0133 | 0.23 ( 0.07, 0.82) | 0.23 ( 0.07, 0.82) | -0.01 (-0.02, 0.00) | | |
| Yes | 140 | 0 | 0 | 140 | 0 | 0 | 1.0000 | 1.00 ( 0.02, 50.05) | 1.00 ( 0.02, 50.75) | 0.00 (-0.01, 0.01) | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Bundle branch block left

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.2665 |
| <45 | 179 | 1 | 0.6 | 178 | 1 | 0.6 | 0.9968 | 1.01 ( 0.06, 15.95) | 1.01 ( 0.06, 16.20) | 0.00 (-0.02, 0.02) | |
| >=45 | 1009 | 12 | 1.2 | 993 | 2 | 0.2 | 0.0080 | 0.17 ( 0.04, 0.75) | 0.17 ( 0.04, 0.75) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 3 | 1.2 | 257 | 1 | 0.4 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 5 | 0.7 | 645 | 1 | 0.2 | | | | | |
| Macroalbuminuria (>300) | 260 | 5 | 1.9 | 261 | 1 | 0.4 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8636 |
| Low, moderate or high | 1018 | 12 | 1.2 | 1001 | 3 | 0.3 | 0.0215 | 0.25 ( 0.07, 0.90) | 0.25 ( 0.07, 0.90) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 1 | 0.6 | 162 | 0 | 0 | 0.4915 | 0.34 ( 0.01, 8.37) | 0.34 ( 0.01, 8.45) | -0.01 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.6293 |
| No | 205 | 3 | 1.5 | 211 | 0 | 0 | 0.1245 | 0.14 (<0.01, 2.67) | 0.14 (<0.01, 2.66) | -0.01 (-0.03, 0.00) | |
| Yes | 983 | 10 | 1.0 | 960 | 3 | 0.3 | 0.0567 | 0.31 ( 0.08, 1.11) | 0.31 ( 0.08, 1.11) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 422 | 6 | 1.4 | 408 | 1 | 0.2 | | | | | |
| Yes | 766 | 7 | 0.9 | 763 | 2 | 0.3 | | | | | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 7 | 1.1 | 589 | 1 | 0.2 | | | | | |
| Yes | 559 | 6 | 1.1 | 582 | 2 | 0.3 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 2 | 0.2 | 0.0080 | 0.17 ( 0.04, 0.75) | 0.17 ( 0.04, 0.75) | -0.01 (-0.01, 0.00) | | |
| Sex | | | | | | | | | | | | 0.9714 |
| Male | 864 | 10 | 1.2 | 837 | 2 | 0.2 | 0.0237 | 0.21 ( 0.05, 0.94) | 0.20 ( 0.04, 0.94) | -0.01 (-0.02, 0.00) | | |
| Female | 324 | 2 | 0.6 | 334 | 0 | 0 | 0.2365 | 0.19 (<0.01, 4.03) | 0.19 (<0.01, 4.03) | -0.01 (-0.02, 0.00) | | |
| Age [years] | | | | | | | | | | | | 0.8165 |
| <65 | 569 | 3 | 0.5 | 547 | 0 | 0 | 0.1433 | 0.15 (<0.01, 2.87) | 0.15 (<0.01, 2.87) | -0.01 (-0.01, 0.00) | | |
| >=65 | 619 | 9 | 1.5 | 624 | 2 | 0.3 | 0.0329 | 0.22 ( 0.05, 1.02) | 0.22 ( 0.05, 1.01) | -0.01 (-0.02, 0.00) | | |
| Region | | | | | | | | | | | | |
| Europe | 468 | 2 | 0.4 | 434 | 0 | 0 | | | | | | |
| North America | 259 | 5 | 1.9 | 241 | 2 | 0.8 | | | | | | |
| Latin America | 177 | 1 | 0.6 | 191 | 0 | 0 | | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | | |
| Asia | 234 | 4 | 1.7 | 251 | 0 | 0 | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | |
| <30 | 554 | 7 | 1.3 | 566 | 0 | 0 | | | | | | |
| >=30 | 634 | 5 | 0.8 | 605 | 2 | 0.3 | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | |
| <130 | 379 | 5 | 1.3 | 382 | 1 | 0.3 | | | | | | |
| >=130 | 809 | 7 | 0.9 | 789 | 1 | 0.1 | | | | | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 500 | 5 | 1.0 | 500 | 2 | 0.4 | | | | | | |
| 75 to <85 | 427 | 5 | 1.2 | 417 | 0 | 0 | | | | | | |
| >=85 | 261 | 2 | 0.8 | 254 | 0 | 0 | | | | | | |
| History of heart failure | | | | | | | | | | | | 0.7872 |
| No | 1048 | 9 | 0.9 | 1031 | 2 | 0.2 | 0.0367 | 0.23 ( 0.05, 1.04) | 0.22 ( 0.05, 1.04) | -0.01 (-0.01, 0.00) | | |
| Yes | 140 | 3 | 2.1 | 140 | 0 | 0 | 0.1309 | 0.14 (<0.01, 2.74) | 0.14 (<0.01, 2.73) | -0.02 (-0.05, 0.01) | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0434 |
| <45 | 179 | 1 | 0.6 | 178 | 2 | 1.1 | 0.5588 | 2.01 ( 0.18, 21.98) | 2.02 ( 0.18, 22.51) | 0.01 (-0.01, 0.02) | |
| >=45 | 1009 | 11 | 1.1 | 993 | 0 | 0 | 0.0016 | 0.04 (<0.01, 0.75) | 0.04 (<0.01, 0.74) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 3 | 1.2 | 257 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 9 | 1.3 | 645 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 2 | 0.8 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0220 |
| Low, moderate or high | 1018 | 12 | 1.2 | 1001 | 0 | 0 | 0.0009 | 0.04 (<0.01, 0.69) | 0.04 (<0.01, 0.68) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 0 | 0 | 162 | 2 | 1.2 | 0.2355 | 5.15 ( 0.25,106.52) | 5.22 ( 0.25,109.53) | 0.01 (-0.01, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.6082 |
| No | 205 | 4 | 2.0 | 211 | 0 | 0 | 0.0669 | 0.11 (<0.01, 1.99) | 0.11 (<0.01, 1.98) | -0.02 (-0.04, 0.00) | |
| Yes | 983 | 8 | 0.8 | 960 | 2 | 0.2 | 0.0622 | 0.26 ( 0.05, 1.20) | 0.25 ( 0.05, 1.20) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6430 |
| No | 422 | 4 | 0.9 | 408 | 0 | 0 | 0.0790 | 0.11 (<0.01, 2.13) | 0.11 (<0.01, 2.12) | -0.01 (-0.02, 0.00) | |
| Yes | 766 | 8 | 1.0 | 763 | 2 | 0.3 | 0.0578 | 0.25 ( 0.05, 1.18) | 0.25 ( 0.05, 1.18) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 5 | 0.8 | 589 | 0 | 0 | | | | | |
| Yes | 559 | 7 | 1.3 | 582 | 2 | 0.3 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Dizziness

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 95 | 8.0 | 1171 | 100 | 8.5 | 0.6320 | 1.07 ( 0.82, 1.40) | 1.07 ( 0.80, 1.44) | 0.01 (-0.02, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Headache

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 67 | 5.6 | 1171 | 53 | 4.5 | 0.2184 | 0.80 ( 0.56, 1.14) | 0.79 ( 0.55, 1.15) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Cerebrovascular accident

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 23 | 1.9 | 1171 | 33 | 2.8 | 0.1594 | 1.46 ( 0.86, | 2.46) | 1.47 ( 0.86, | 2.52) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Diabetic neuropathy

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 28 | 2.4 | 1171 | 26 | 2.2 | 0.8245 | 0.94 ( 0.56, 1.60) | 0.94 ( 0.55, 1.61) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Carpal tunnel syndrome

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 24 | 2.0 | 1171 | 14 | 1.2 | 0.1117 | 0.59 ( 0.31, | 1.14) | 0.59 ( 0.30, | 1.14) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Neuropathy peripheral

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 17 | 1.4 | 1171 | 22 | 1.9 | 0.3938 | 1.31 ( 0.70, | 2.46) | 1.32 ( 0.70, | 2.50) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Hypoaesthesia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 21 | 1.8 | 1171 | 17 | 1.5 | 0.5423 | 0.82 ( 0.44, 1.55) | 0.82 ( 0.43, 1.56) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Sciatica

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 21 | 1.8 | 1171 | 11 | 0.9 | 0.0821 | 0.53 ( 0.26, | 1.10) | 0.53 ( 0.25, | 1.10) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Syncope

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 20 | 1.7 | 1171 | 20 | 1.7 | 0.9633 | 1.01 ( 0.55, 1.88) | 1.01 ( 0.54, 1.90) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Transient ischaemic attack

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 19 | 1.6 | 1171 | 16 | 1.4 | 0.6398 | 0.85 ( 0.44, 1.65) | 0.85 ( 0.44, 1.67) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Tremor

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 10 | 0.8 | 1171 | 16 | 1.4 | 0.2224 | 1.62 ( 0.74, 3.56) | 1.63 ( 0.74, 3.61) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Carotid artery stenosis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 16 | 1.3 | 1171 | 6 | 0.5 | 0.0350 | 0.38 ( 0.15, | 0.97) | 0.38 ( 0.15, | 0.97) | -0.01 (-0.02, | 0.00) | |
| Sex | | | | | | | | | | | | | | 0.8363 |
| Male | 864 | 14 | 1.6 | 837 | 5 | 0.6 | 0.0447 | 0.37 ( 0.13, | 1.02) | 0.36 ( 0.13, | 1.02) | -0.01 (-0.02, | 0.00) | |
| Female | 324 | 2 | 0.6 | 334 | 1 | 0.3 | 0.5451 | 0.49 ( 0.04, | 5.32) | 0.48 ( 0.04, | 5.36) | 0.00 (-0.01, | 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.5619 |
| <65 | 569 | 6 | 1.1 | 547 | 3 | 0.5 | 0.3447 | 0.52 ( 0.13, | 2.07) | 0.52 ( 0.13, | 2.08) | -0.01 (-0.02, | 0.01) | |
| >=65 | 619 | 10 | 1.6 | 624 | 3 | 0.5 | 0.0493 | 0.30 ( 0.08, | 1.08) | 0.29 ( 0.08, | 1.07) | -0.01 (-0.02, | 0.00) | |
| Region | | | | | | | | | | | | | | 0.3243 |
| Europe | 468 | 10 | 2.1 | 434 | 1 | 0.2 | 0.0092 | 0.11 ( 0.01, | 0.84) | 0.11 ( 0.01, | 0.83) | -0.02 (-0.03,-0.01) | | |
| North America | 259 | 2 | 0.8 | 241 | 3 | 1.2 | 0.5956 | 1.61 ( 0.27, | 9.56) | 1.62 ( 0.27, | 9.78) | 0.00 (-0.01, | 0.02) | |
| Latin America | 177 | 2 | 1.1 | 191 | 2 | 1.0 | 0.9390 | 0.93 ( 0.13, | 6.51) | 0.93 ( 0.13, | 6.64) | 0.00 (-0.02, | 0.02) | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | 0.9697 | 0.93 ( 0.02, | 45.87) | 0.93 ( 0.02, | 47.58) | 0.00 (-0.04, | 0.04) | |
| Asia | 234 | 2 | 0.9 | 251 | 0 | 0 | 0.2226 | 0.19 (<0.01, | 3.86) | 0.18 (<0.01, | 3.87) | -0.01 (-0.02, | 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1088 |
| <30 | 554 | 9 | 1.6 | 566 | 1 | 0.2 | 0.0100 | 0.11 ( 0.01, | 0.86) | 0.11 ( 0.01, | 0.85) | -0.01 (-0.03, | 0.00) | |
| >=30 | 634 | 7 | 1.1 | 605 | 5 | 0.8 | 0.6179 | 0.75 ( 0.24, | 2.35) | 0.75 ( 0.24, | 2.36) | 0.00 (-0.01, | 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7194 |
| <130 | 379 | 4 | 1.1 | 382 | 2 | 0.5 | 0.4069 | 0.50 ( 0.09, | 2.69) | 0.49 ( 0.09, | 2.71) | -0.01 (-0.02, | 0.01) | |
| >=130 | 809 | 12 | 1.5 | 789 | 4 | 0.5 | 0.0500 | 0.34 ( 0.11, | 1.06) | 0.34 ( 0.11, | 1.05) | -0.01 (-0.02, | 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4655 |
| <75 | 500 | 8 | 1.6 | 500 | 3 | 0.6 | 0.1295 | 0.38 ( 0.10, | 1.41) | 0.37 ( 0.10, | 1.41) | -0.01 (-0.02, | 0.00) | |
| 75 to <85 | 427 | 6 | 1.4 | 417 | 1 | 0.2 | 0.0620 | 0.17 ( 0.02, | 1.41) | 0.17 ( 0.02, | 1.41) | -0.01 (-0.02, | 0.00) | |
| >=85 | 261 | 2 | 0.8 | 254 | 2 | 0.8 | 0.9782 | 1.03 ( 0.15, | 7.24) | 1.03 ( 0.14, | 7.35) | 0.00 (-0.01, | 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.9069 |
| No | 1048 | 15 | 1.4 | 1031 | 6 | 0.6 | 0.0528 | 0.41 ( 0.16, | 1.04) | 0.40 ( 0.16, | 1.04) | -0.01 (-0.02, | 0.00) | |
| Yes | 140 | 1 | 0.7 | 140 | 0 | 0 | 0.4779 | 0.33 ( 0.01, | 8.11) | 0.33 ( 0.01, | 8.19) | -0.01 (-0.03, | 0.01) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Carotid artery stenosis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.4940 |
| <45 | 179 | 5 | 2.8 | 178 | 1 | 0.6 | 0.1010 | 0.20 ( 0.02, 1.70) | 0.20 ( 0.02, 1.70) | -0.02 (-0.05, 0.00) | |
| >=45 | 1009 | 11 | 1.1 | 993 | 5 | 0.5 | 0.1405 | 0.46 ( 0.16, 1.32) | 0.46 ( 0.16, 1.33) | -0.01 (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.3269 |
| Normal (<30) | 250 | 6 | 2.4 | 257 | 1 | 0.4 | 0.0524 | 0.16 ( 0.02, 1.34) | 0.16 ( 0.02, 1.33) | -0.02 (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 7 | 1.0 | 645 | 5 | 0.8 | 0.6163 | 0.75 ( 0.24, 2.34) | 0.75 ( 0.24, 2.36) | 0.00 (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 260 | 3 | 1.2 | 261 | 0 | 0 | 0.1311 | 0.14 (<0.01, 2.74) | 0.14 (<0.01, 2.74) | -0.01 (-0.03, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.4587 |
| Low, moderate or high | 1018 | 15 | 1.5 | 1001 | 5 | 0.5 | 0.0271 | 0.34 ( 0.12, 0.93) | 0.34 ( 0.12, 0.93) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 1 | 0.6 | 162 | 1 | 0.6 | 0.9828 | 1.03 ( 0.07, 16.34) | 1.03 ( 0.06, 16.62) | 0.00 (-0.02, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.5013 |
| No | 205 | 3 | 1.5 | 211 | 2 | 0.9 | 0.6295 | 0.65 ( 0.11, 3.84) | 0.64 ( 0.11, 3.90) | -0.01 (-0.03, 0.02) | |
| Yes | 983 | 13 | 1.3 | 960 | 4 | 0.4 | 0.0321 | 0.32 ( 0.10, 0.96) | 0.31 ( 0.10, 0.96) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.5160 |
| No | 422 | 5 | 1.2 | 408 | 1 | 0.2 | 0.1101 | 0.21 ( 0.02, 1.76) | 0.20 ( 0.02, 1.76) | -0.01 (-0.02, 0.00) | |
| Yes | 766 | 11 | 1.4 | 763 | 5 | 0.7 | 0.1336 | 0.46 ( 0.16, 1.31) | 0.45 ( 0.16, 1.31) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.6741 |
| No | 629 | 10 | 1.6 | 589 | 3 | 0.5 | 0.0667 | 0.32 ( 0.09, 1.16) | 0.32 ( 0.09, 1.16) | -0.01 (-0.02, 0.00) | |
| Yes | 559 | 6 | 1.1 | 582 | 3 | 0.5 | 0.2869 | 0.48 ( 0.12, 1.91) | 0.48 ( 0.12, 1.92) | -0.01 (-0.02, 0.00) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Paraesthesia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 14 | 1.2 | 0.8825 | 0.95 ( 0.46, 1.95) | 0.95 ( 0.45, 1.97) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 13 | 1.1 | 0.8761 | 0.94 ( 0.44, 2.00) | 0.94 ( 0.44, 2.01) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Back pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 83 | 7.0 | 1171 | 83 | 7.1 | 0.9233 | 1.01 ( 0.76, 1.36) | 1.02 ( 0.74, 1.39) | 0.00 (-0.02, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Arthralgia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 73 | 6.1 | 1171 | 63 | 5.4 | 0.4256 | 0.88 ( 0.63, | 1.21) | 0.87 ( 0.61, | 1.23) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Pain in extremity

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 72 | 6.1 | 1171 | 54 | 4.6 | 0.1176 | 0.76 ( 0.54, | 1.07) | 0.75 ( 0.52, | 1.08) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Osteoarthritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 49 | 4.1 | 1171 | 39 | 3.3 | 0.3089 | 0.81 ( 0.53, 1.22) | 0.80 ( 0.52, 1.23) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Musculoskeletal pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 43 | 3.6 | 1171 | 36 | 3.1 | 0.4618 | 0.85 ( 0.55, | 1.31) | 0.84 ( 0.54, | 1.32) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Muscle spasms

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 39 | 3.3 | 1171 | 29 | 2.5 | 0.2419 | 0.75 ( 0.47, 1.21) | 0.75 ( 0.46, 1.22) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Myalgia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 30 | 2.5 | 1171 | 33 | 2.8 | 0.6591 | 1.12 ( 0.69, | 1.82) | 1.12 ( 0.68, | 1.85) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Neck pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 19 | 1.6 | 1171 | 15 | 1.3 | 0.5165 | 0.80 ( 0.41, | 1.57) | 0.80 ( 0.40, | 1.58) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Spinal osteoarthritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 10 | 0.8 | 1171 | 16 | 1.4 | 0.2224 | 1.62 ( 0.74, 3.56) | 1.63 ( 0.74, 3.61) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Rotator cuff syndrome

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 10 | 0.8 | 1171 | 13 | 1.1 | 0.5071 | 1.32 ( 0.58, | 3.00) | 1.32 ( 0.58, | 3.03) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Arthritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 11 | 0.9 | 0.7078 | 0.86 ( 0.39, | 1.91) | 0.86 ( 0.38, | 1.92) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Tendonitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 11 | 0.9 | 0.7078 | 0.86 ( 0.39, | 1.91) | 0.86 ( 0.38, | 1.92) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Trigger finger

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 10 | 0.8 | 1171 | 12 | 1.0 | 0.6438 | 1.22 ( 0.53, | 2.81) | 1.22 ( 0.52, | 2.83) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Muscular weakness

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 8 | 0.7 | 0.3865 | 0.68 ( 0.28, 1.65) | 0.67 ( 0.27, 1.66) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal impairment

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 57 | 4.8 | 1171 | 60 | 5.1 | 0.7155 | 1.07 ( 0.75, 1.52) | 1.07 ( 0.74, 1.55) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 43 | 3.6 | 1171 | 19 | 1.6 | 0.0024 | 0.45 | ( 0.26, 0.76) | 0.44 | ( 0.25, 0.76) | -0.02 | (-0.03,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.9692 |
| Male | 864 | 32 | 3.7 | 837 | 14 | 1.7 | 0.0098 | 0.45 | ( 0.24, 0.84) | 0.44 | ( 0.23, 0.83) | -0.02 | (-0.04,-0.01) | |
| Female | 324 | 11 | 3.4 | 334 | 5 | 1.5 | 0.1140 | 0.44 | ( 0.15, 1.26) | 0.43 | ( 0.15, 1.26) | -0.02 | (-0.04, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.4470 |
| <65 | 569 | 16 | 2.8 | 547 | 5 | 0.9 | 0.0197 | 0.33 | ( 0.12, 0.88) | 0.32 | ( 0.12, 0.88) | -0.02 | (-0.03, 0.00) | |
| >=65 | 619 | 27 | 4.4 | 624 | 14 | 2.2 | 0.0365 | 0.51 | ( 0.27, 0.97) | 0.50 | ( 0.26, 0.97) | -0.02 | (-0.04, 0.00) | |
| Region | | | | | | | | | | | | | | 0.7014 |
| Europe | 468 | 16 | 3.4 | 434 | 10 | 2.3 | 0.3175 | 0.67 | ( 0.31, 1.47) | 0.67 | ( 0.30, 1.48) | -0.01 | (-0.03, 0.01) | |
| North America | 259 | 15 | 5.8 | 241 | 4 | 1.7 | 0.0158 | 0.29 | ( 0.10, 0.85) | 0.27 | ( 0.09, 0.84) | -0.04 | (-0.07,-0.01) | |
| Latin America | 177 | 3 | 1.7 | 191 | 2 | 1.0 | 0.5917 | 0.62 | ( 0.10, 3.65) | 0.61 | ( 0.10, 3.72) | -0.01 | (-0.03, 0.02) | |
| Africa | 50 | 5 | 10.0 | 54 | 2 | 3.7 | 0.2004 | 0.37 | ( 0.08, 1.82) | 0.35 | ( 0.06, 1.87) | -0.06 | (-0.16, 0.03) | |
| Asia | 234 | 4 | 1.7 | 251 | 1 | 0.4 | 0.1532 | 0.23 | ( 0.03, 2.07) | 0.23 | ( 0.03, 2.07) | -0.01 | (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6535 |
| <30 | 554 | 20 | 3.6 | 566 | 8 | 1.4 | 0.0186 | 0.39 | ( 0.17, 0.88) | 0.38 | ( 0.17, 0.88) | -0.02 | (-0.04, 0.00) | |
| >=30 | 634 | 23 | 3.6 | 605 | 11 | 1.8 | 0.0513 | 0.50 | ( 0.25, 1.02) | 0.49 | ( 0.24, 1.02) | -0.02 | (-0.04, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2356 |
| <130 | 379 | 10 | 2.6 | 382 | 2 | 0.5 | 0.0192 | 0.20 | ( 0.04, 0.90) | 0.19 | ( 0.04, 0.89) | -0.02 | (-0.04, 0.00) | |
| >=130 | 809 | 33 | 4.1 | 789 | 17 | 2.2 | 0.0272 | 0.53 | ( 0.30, 0.94) | 0.52 | ( 0.29, 0.94) | -0.02 | (-0.04, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3381 |
| <75 | 500 | 20 | 4.0 | 500 | 8 | 1.6 | 0.0214 | 0.40 | ( 0.18, 0.90) | 0.39 | ( 0.17, 0.89) | -0.02 | (-0.04, 0.00) | |
| 75 to <85 | 427 | 18 | 4.2 | 417 | 6 | 1.4 | 0.0153 | 0.34 | ( 0.14, 0.85) | 0.33 | ( 0.13, 0.84) | -0.03 | (-0.05,-0.01) | |
| >=85 | 261 | 5 | 1.9 | 254 | 5 | 2.0 | 0.9654 | 1.03 | ( 0.30, 3.51) | 1.03 | ( 0.29, 3.59) | 0.00 | (-0.02, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.4147 |
| No | 1048 | 35 | 3.3 | 1031 | 17 | 1.6 | 0.0136 | 0.49 | ( 0.28, 0.88) | 0.49 | ( 0.27, 0.87) | -0.02 | (-0.03, 0.00) | |
| Yes | 140 | 8 | 5.7 | 140 | 2 | 1.4 | 0.0533 | 0.25 | ( 0.05, 1.16) | 0.24 | ( 0.05, 1.15) | -0.04 | (-0.09, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.9627 |
| <45 | 179 | 16 | 8.9 | 178 | 7 | 3.9 | 0.0541 | 0.44 ( 0.19, | 1.04) | 0.42 ( 0.17, | 1.04) | -0.05 (-0.10, 0.00) | |
| >=45 | 1009 | 27 | 2.7 | 993 | 12 | 1.2 | 0.0175 | 0.45 ( 0.23, | 0.89) | 0.44 ( 0.22, | 0.88) | -0.01 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.7179 |
| Normal (<30) | 250 | 15 | 6.0 | 257 | 5 | 1.9 | 0.0190 | 0.32 ( 0.12, | 0.88) | 0.31 ( 0.11, | 0.87) | -0.04 (-0.07,-0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 15 | 2.2 | 645 | 8 | 1.2 | 0.1729 | 0.56 ( 0.24, | 1.31) | 0.55 ( 0.23, | 1.31) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 260 | 13 | 5.0 | 261 | 6 | 2.3 | 0.1001 | 0.46 ( 0.18, | 1.19) | 0.45 ( 0.17, | 1.19) | -0.03 (-0.06, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.7191 |
| Low, moderate or high | 1018 | 29 | 2.8 | 1001 | 12 | 1.2 | 0.0086 | 0.42 ( 0.22, | 0.82) | 0.41 ( 0.21, | 0.82) | -0.02 (-0.03, 0.00) | |
| Very high | 167 | 14 | 8.4 | 162 | 7 | 4.3 | 0.1318 | 0.52 ( 0.21, | 1.24) | 0.49 ( 0.19, | 1.26) | -0.04 (-0.09, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.9030 |
| No | 205 | 6 | 2.9 | 211 | 3 | 1.4 | 0.2915 | 0.49 ( 0.12, | 1.92) | 0.48 ( 0.12, | 1.94) | -0.02 (-0.04, 0.01) | |
| Yes | 983 | 37 | 3.8 | 960 | 16 | 1.7 | 0.0045 | 0.44 ( 0.25, | 0.79) | 0.43 ( 0.24, | 0.78) | -0.02 (-0.04,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.4199 |
| No | 422 | 11 | 2.6 | 408 | 3 | 0.7 | 0.0363 | 0.28 ( 0.08, | >1.00) | 0.28 ( 0.08, | 1.00) | -0.02 (-0.04, 0.00) | |
| Yes | 766 | 32 | 4.2 | 763 | 16 | 2.1 | 0.0197 | 0.50 ( 0.28, | 0.91) | 0.49 ( 0.27, | 0.90) | -0.02 (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.9411 |
| No | 629 | 15 | 2.4 | 589 | 6 | 1.0 | 0.0672 | 0.43 ( 0.17, | 1.09) | 0.42 ( 0.16, | 1.09) | -0.01 (-0.03, 0.00) | |
| Yes | 559 | 28 | 5.0 | 582 | 13 | 2.2 | 0.0118 | 0.45 ( 0.23, | 0.85) | 0.43 ( 0.22, | 0.85) | -0.03 (-0.05,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 37 | 3.1 | 1171 | 22 | 1.9 | 0.0546 | 0.60 ( 0.36, 1.02) | 0.60 ( 0.35, 1.02) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Diabetic nephropathy

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 36 | 3.0 | 1171 | 27 | 2.3 | 0.2751 | 0.76 ( 0.47, | 1.25) | 0.76 ( 0.46, | 1.25) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Chronic kidney disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 35 | 2.9 | 1171 | 25 | 2.1 | 0.2109 | 0.72 ( 0.44, 1.20) | 0.72 ( 0.43, 1.21) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Proteinuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 33 | 2.8 | 1171 | 29 | 2.5 | 0.6474 | 0.89 ( 0.54, 1.46) | 0.89 ( 0.54, 1.47) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Pollakiuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 21 | 1.8 | 1171 | 28 | 2.4 | 0.2884 | 1.35 ( 0.77, | 2.37) | 1.36 ( 0.77, | 2.41) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Haematuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 25 | 2.1 | 1171 | 22 | 1.9 | 0.6950 | 0.89 ( 0.51, 1.57) | 0.89 ( 0.50, 1.59) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Dysuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 5 | 0.4 | 1171 | 20 | 1.7 | 0.0023 | 4.06 ( 1.53, 10.78) | 4.11 ( 1.54, 10.99) | 0.01 ( 0.00, 0.02) | |
| Sex | | | | | | | | | | | 0.1338 |
| Male | 864 | 2 | 0.2 | 837 | 15 | 1.8 | 0.0012 | 7.74 ( 1.78, 33.75) | 7.86 ( 1.79, 34.50) | 0.02 ( 0.01, 0.03) | |
| Female | 324 | 3 | 0.9 | 334 | 5 | 1.5 | 0.5040 | 1.62 ( 0.39, 6.71) | 1.63 ( 0.39, 6.86) | 0.01 (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | 0.3988 |
| <65 | 569 | 2 | 0.4 | 547 | 12 | 2.2 | 0.0057 | 6.24 ( 1.40, 27.76) | 6.36 ( 1.42, 28.54) | 0.02 ( 0.01, 0.03) | |
| >=65 | 619 | 3 | 0.5 | 624 | 8 | 1.3 | 0.1334 | 2.65 ( 0.71, 9.92) | 2.67 ( 0.70, 10.10) | 0.01 ( 0.00, 0.02) | |
| Region | | | | | | | | | | | |
| Europe | 468 | 1 | 0.2 | 434 | 5 | 1.2 | | | | | |
| North America | 259 | 2 | 0.8 | 241 | 1 | 0.4 | | | | | |
| Latin America | 177 | 2 | 1.1 | 191 | 5 | 2.6 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 3 | 5.6 | | | | | |
| Asia | 234 | 0 | 0 | 251 | 6 | 2.4 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.7878 |
| <30 | 554 | 3 | 0.5 | 566 | 11 | 1.9 | 0.0347 | 3.59 ( 1.01, 12.80) | 3.64 ( 1.01, 13.12) | 0.01 ( 0.00, 0.03) | |
| >=30 | 634 | 2 | 0.3 | 605 | 9 | 1.5 | 0.0279 | 4.72 ( 1.02, 21.74) | 4.77 ( 1.03, 22.18) | 0.01 ( 0.00, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.2598 |
| <130 | 379 | 1 | 0.3 | 382 | 10 | 2.6 | 0.0065 | 9.92 ( 1.28, 77.12) | 10.16 ( 1.29, 79.77) | 0.02 ( 0.01, 0.04) | |
| >=130 | 809 | 4 | 0.5 | 789 | 10 | 1.3 | 0.0974 | 2.56 ( 0.81, 8.14) | 2.58 ( 0.81, 8.27) | 0.01 ( 0.00, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.6024 |
| <75 | 500 | 3 | 0.6 | 500 | 8 | 1.6 | 0.1295 | 2.67 ( 0.71, 9.99) | 2.69 ( 0.71, 10.21) | 0.01 ( 0.00, 0.02) | |
| 75 to <85 | 427 | 1 | 0.2 | 417 | 9 | 2.2 | 0.0098 | 9.22 ( 1.17, 72.42) | 9.40 ( 1.19, 74.50) | 0.02 ( 0.00, 0.03) | |
| >=85 | 261 | 1 | 0.4 | 254 | 3 | 1.2 | 0.3024 | 3.08 ( 0.32, 29.44) | 3.11 ( 0.32, 30.07) | 0.01 (-0.01, 0.02) | |
| History of heart failure | | | | | | | | | | | 0.8821 |
| No | 1048 | 5 | 0.5 | 1031 | 19 | 1.8 | 0.0036 | 3.86 ( 1.45, 10.31) | 3.92 ( 1.46, 10.53) | 0.01 ( 0.00, 0.02) | |
| Yes | 140 | 0 | 0 | 140 | 1 | 0.7 | 0.4779 | 3.00 ( 0.12, 73.02) | 3.02 ( 0.12, 74.81) | 0.01 (-0.01, 0.03) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Dysuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0625 |
| <45 | 179 | 2 | 1.1 | 178 | 1 | 0.6 | 0.5653 | 0.50 ( 0.05, 5.50) | 0.50 ( 0.04, 5.56) | -0.01 (-0.02, 0.01) | |
| >=45 | 1009 | 3 | 0.3 | 993 | 19 | 1.9 | 0.0005 | 6.44 ( 1.91, 21.68) | 6.54 ( 1.93, 22.18) | 0.02 ( 0.01, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.4980 |
| Normal (<30) | 250 | 2 | 0.8 | 257 | 3 | 1.2 | 0.6756 | 1.46 ( 0.25, 8.66) | 1.46 ( 0.24, 8.84) | 0.00 (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 3 | 0.4 | 645 | 12 | 1.9 | 0.0153 | 4.19 ( 1.19, 14.77) | 4.25 ( 1.19, 15.12) | 0.01 ( 0.00, 0.03) | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 4 | 1.5 | 0.0729 | 8.97 ( 0.49,165.69) | 9.10 ( 0.49,169.97) | 0.02 ( 0.00, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8062 |
| Low, moderate or high | 1018 | 5 | 0.5 | 1001 | 17 | 1.7 | 0.0090 | 3.46 ( 1.28, 9.34) | 3.50 ( 1.29, 9.52) | 0.01 ( 0.00, 0.02) | |
| Very high | 167 | 0 | 0 | 162 | 2 | 1.2 | 0.2355 | 5.15 ( 0.25,106.52) | 5.22 ( 0.25,109.53) | 0.01 (-0.01, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.4244 |
| No | 205 | 0 | 0 | 211 | 5 | 2.4 | 0.0433 | 10.69 ( 0.59,192.08) | 10.95 ( 0.60,199.24) | 0.02 ( 0.00, 0.05) | |
| Yes | 983 | 5 | 0.5 | 960 | 15 | 1.6 | 0.0214 | 3.07 ( 1.12, 8.42) | 3.10 ( 1.12, 8.58) | 0.01 ( 0.00, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.4015 |
| No | 422 | 1 | 0.2 | 408 | 8 | 2.0 | 0.0165 | 8.27 ( 1.04, 65.86) | 8.42 ( 1.05, 67.62) | 0.02 ( 0.00, 0.03) | |
| Yes | 766 | 4 | 0.5 | 763 | 12 | 1.6 | 0.0435 | 3.01 ( 0.98, 9.30) | 3.04 ( 0.98, 9.48) | 0.01 ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | 0.2826 |
| No | 629 | 1 | 0.2 | 589 | 9 | 1.5 | 0.0081 | 9.61 ( 1.22, 75.63) | 9.74 ( 1.23, 77.15) | 0.01 ( 0.00, 0.02) | |
| Yes | 559 | 4 | 0.7 | 582 | 11 | 1.9 | 0.0817 | 2.64 ( 0.85, 8.25) | 2.67 ( 0.85, 8.44) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Nephrolithiasis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 20 | 1.7 | 1171 | 13 | 1.1 | 0.2358 | 0.66 ( 0.33, 1.32) | 0.66 ( 0.32, 1.32) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Polyuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 6 | 0.5 | 1171 | 18 | 1.5 | 0.0125 | 3.04 ( 1.21, 7.64) | 3.08 ( 1.22, 7.78) | 0.01 ( 0.00, 0.02) | |
| Sex | | | | | | | | | | | 0.3598 |
| Male | 864 | 4 | 0.5 | 837 | 15 | 1.8 | 0.0091 | 3.87 ( 1.29, 11.62) | 3.92 ( 1.30, 11.87) | 0.01 ( 0.00, 0.02) | |
| Female | 324 | 2 | 0.6 | 334 | 3 | 0.9 | 0.6782 | 1.46 ( 0.24, 8.65) | 1.46 ( 0.24, 8.79) | 0.00 (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | 0.6687 |
| <65 | 569 | 3 | 0.5 | 547 | 7 | 1.3 | 0.1824 | 2.43 ( 0.63, 9.34) | 2.45 ( 0.63, 9.51) | 0.01 ( 0.00, 0.02) | |
| >=65 | 619 | 3 | 0.5 | 624 | 11 | 1.8 | 0.0328 | 3.64 ( 1.02, 12.97) | 3.68 ( 1.02, 13.27) | 0.01 ( 0.00, 0.02) | |
| Region | | | | | | | | | | | |
| Europe | 468 | 1 | 0.2 | 434 | 7 | 1.6 | | | | | |
| North America | 259 | 1 | 0.4 | 241 | 4 | 1.7 | | | | | |
| Latin America | 177 | 2 | 1.1 | 191 | 5 | 2.6 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | |
| Asia | 234 | 2 | 0.9 | 251 | 2 | 0.8 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.1824 |
| <30 | 554 | 3 | 0.5 | 566 | 4 | 0.7 | 0.7258 | 1.31 ( 0.29, 5.80) | 1.31 ( 0.29, 5.87) | 0.00 (-0.01, 0.01) | |
| >=30 | 634 | 3 | 0.5 | 605 | 14 | 2.3 | 0.0054 | 4.89 ( 1.41, 16.93) | 4.98 ( 1.42, 17.43) | 0.02 ( 0.01, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.3069 |
| <130 | 379 | 3 | 0.8 | 382 | 5 | 1.3 | 0.4841 | 1.65 ( 0.40, 6.87) | 1.66 ( 0.39, 7.01) | 0.01 (-0.01, 0.02) | |
| >=130 | 809 | 3 | 0.4 | 789 | 13 | 1.6 | 0.0104 | 4.44 ( 1.27, 15.53) | 4.50 ( 1.28, 15.86) | 0.01 ( 0.00, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.3424 |
| <75 | 500 | 2 | 0.4 | 500 | 12 | 2.4 | 0.0071 | 6.00 ( 1.35, 26.67) | 6.12 ( 1.36, 27.50) | 0.02 ( 0.01, 0.03) | |
| 75 to <85 | 427 | 2 | 0.5 | 417 | 4 | 1.0 | 0.3961 | 2.05 ( 0.38, 11.12) | 2.06 ( 0.37, 11.30) | 0.00 (-0.01, 0.02) | |
| >=85 | 261 | 2 | 0.8 | 254 | 2 | 0.8 | 0.9782 | 1.03 ( 0.15, 7.24) | 1.03 ( 0.14, 7.35) | 0.00 (-0.01, 0.02) | |
| History of heart failure | | | | | | | | | | | 0.9808 |
| No | 1048 | 6 | 0.6 | 1031 | 17 | 1.6 | 0.0190 | 2.88 ( 1.14, 7.28) | 2.91 ( 1.14, 7.41) | 0.01 ( 0.00, 0.02) | |
| Yes | 140 | 0 | 0 | 140 | 1 | 0.7 | 0.4779 | 3.00 ( 0.12, 73.02) | 3.02 ( 0.12, 74.81) | 0.01 (-0.01, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Polyuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.7164 |
| <45 | 179 | 1 | 0.6 | 178 | 2 | 1.1 | 0.5588 | 2.01 ( 0.18, 21.98) | 2.02 ( 0.18, 22.51) | 0.01 (-0.01, 0.02) | |
| >=45 | 1009 | 5 | 0.5 | 993 | 16 | 1.6 | 0.0143 | 3.25 ( 1.20, 8.84) | 3.29 ( 1.20, 9.01) | 0.01 ( 0.00, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.2979 |
| Normal (<30) | 250 | 0 | 0 | 257 | 4 | 1.6 | 0.0772 | 8.76 ( 0.47,161.79) | 8.89 ( 0.48,166.05) | 0.02 ( 0.00, 0.03) | |
| Microalbuminuria (30 to <=300) | 675 | 3 | 0.4 | 645 | 11 | 1.7 | 0.0254 | 3.84 ( 1.08, 13.69) | 3.89 ( 1.08, 13.99) | 0.01 ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 260 | 3 | 1.2 | 261 | 3 | 1.1 | 0.9962 | 1.00 ( 0.20, 4.89) | 1.00 ( 0.20, 4.98) | 0.00 (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.1124 |
| Low, moderate or high | 1018 | 4 | 0.4 | 1001 | 17 | 1.7 | 0.0038 | 4.32 ( 1.46, 12.80) | 4.38 ( 1.47, 13.06) | 0.01 ( 0.00, 0.02) | |
| Very high | 167 | 2 | 1.2 | 162 | 1 | 0.6 | 0.5798 | 0.52 ( 0.05, 5.63) | 0.51 ( 0.05, 5.71) | -0.01 (-0.03, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.6929 |
| No | 205 | 1 | 0.5 | 211 | 2 | 0.9 | 0.5793 | 1.94 ( 0.18, 21.26) | 1.95 ( 0.18, 21.70) | 0.00 (-0.01, 0.02) | |
| Yes | 983 | 5 | 0.5 | 960 | 16 | 1.7 | 0.0136 | 3.28 ( 1.21, 8.91) | 3.32 ( 1.21, 9.09) | 0.01 ( 0.00, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.0637 |
| No | 422 | 3 | 0.7 | 408 | 2 | 0.5 | 0.6812 | 0.69 ( 0.12, 4.11) | 0.69 ( 0.11, 4.14) | 0.00 (-0.01, 0.01) | |
| Yes | 766 | 3 | 0.4 | 763 | 16 | 2.1 | 0.0026 | 5.35 ( 1.57, 18.30) | 5.45 ( 1.58, 18.77) | 0.02 ( 0.01, 0.03) | |
| Baseline use of diuretics | | | | | | | | | | | 0.0675 |
| No | 629 | 5 | 0.8 | 589 | 6 | 1.0 | 0.6800 | 1.28 ( 0.39, 4.18) | 1.28 ( 0.39, 4.23) | 0.00 (-0.01, 0.01) | |
| Yes | 559 | 1 | 0.2 | 582 | 12 | 2.1 | 0.0027 | 11.53 ( 1.50, 88.35) | 11.75 ( 1.52, 90.65) | 0.02 ( 0.01, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Microalbuminuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 18 | 1.5 | 1171 | 12 | 1.0 | 0.2879 | 0.68 ( 0.33, 1.40) | 0.67 ( 0.32, 1.40) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Nephropathy

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 16 | 1.3 | 1171 | 10 | 0.9 | 0.2517 | 0.63 ( 0.29, 1.39) | 0.63 ( 0.29, 1.40) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Urinary retention

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 8 | 0.7 | 0.2108 | 0.58 ( 0.24, 1.38) | 0.58 ( 0.24, 1.38) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Nocturia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 9 | 0.8 | 1171 | 13 | 1.1 | 0.3730 | 1.47 ( 0.63, 3.42) | 1.47 ( 0.63, 3.45) | 0.00 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal cyst

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 10 | 0.9 | 0.5526 | 0.78 ( 0.34, 1.77) | 0.78 ( 0.34, 1.78) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood creatinine increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 54 | 4.5 | 1171 | 39 | 3.3 | 0.1295 | 0.73 ( 0.49, 1.10) | 0.72 ( 0.48, 1.10) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood creatine phosphokinase increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 47 | 4.0 | 1171 | 47 | 4.0 | 0.9432 | 1.01 ( 0.68, 1.51) | 1.02 ( 0.67, 1.53) | 0.00 (-0.02, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Glycosylated haemoglobin increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 41 | 3.5 | 1171 | 18 | 1.5 | 0.0029 | 0.45 | ( 0.26, 0.77) | 0.44 | ( 0.25, 0.76) | -0.02 | (-0.03,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.1513 |
| Male | 864 | 27 | 3.1 | 837 | 15 | 1.8 | 0.0766 | 0.57 | ( 0.31, 1.07) | 0.57 | ( 0.30, 1.07) | -0.01 | (-0.03, 0.00) | |
| Female | 324 | 14 | 4.3 | 334 | 3 | 0.9 | 0.0057 | 0.21 | ( 0.06, 0.72) | 0.20 | ( 0.06, 0.71) | -0.03 | (-0.06,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.0965 |
| <65 | 569 | 32 | 5.6 | 547 | 10 | 1.8 | 0.0009 | 0.33 | ( 0.16, 0.65) | 0.31 | ( 0.15, 0.64) | -0.04 | (-0.06,-0.02) | |
| >=65 | 619 | 9 | 1.5 | 624 | 8 | 1.3 | 0.7942 | 0.88 | ( 0.34, 2.27) | 0.88 | ( 0.34, 2.30) | 0.00 | (-0.01, 0.01) | |
| Region | | | | | | | | | | | | | | 0.7125 |
| Europe | 468 | 16 | 3.4 | 434 | 9 | 2.1 | 0.2189 | 0.61 | ( 0.27, 1.36) | 0.60 | ( 0.26, 1.37) | -0.01 | (-0.03, 0.01) | |
| North America | 259 | 5 | 1.9 | 241 | 3 | 1.2 | 0.5415 | 0.64 | ( 0.16, 2.67) | 0.64 | ( 0.15, 2.71) | -0.01 | (-0.03, 0.01) | |
| Latin America | 177 | 2 | 1.1 | 191 | 1 | 0.5 | 0.5181 | 0.46 | ( 0.04, 5.07) | 0.46 | ( 0.04, 5.12) | -0.01 | (-0.02, 0.01) | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | 0.9697 | 0.93 | ( 0.02, 45.87) | 0.93 | ( 0.02, 47.58) | 0.00 | (-0.04, 0.04) | |
| Asia | 234 | 18 | 7.7 | 251 | 5 | 2.0 | 0.0032 | 0.26 | ( 0.10, 0.69) | 0.24 | ( 0.09, 0.67) | -0.06 | (-0.10,-0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0685 |
| <30 | 554 | 16 | 2.9 | 566 | 12 | 2.1 | 0.4105 | 0.73 | ( 0.35, 1.54) | 0.73 | ( 0.34, 1.55) | -0.01 | (-0.03, 0.01) | |
| >=30 | 634 | 25 | 3.9 | 605 | 6 | 1.0 | 0.0009 | 0.25 | ( 0.10, 0.61) | 0.24 | ( 0.10, 0.60) | -0.03 | (-0.05,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9099 |
| <130 | 379 | 15 | 4.0 | 382 | 7 | 1.8 | 0.0802 | 0.46 | ( 0.19, 1.12) | 0.45 | ( 0.18, 1.12) | -0.02 | (-0.05, 0.00) | |
| >=130 | 809 | 26 | 3.2 | 789 | 11 | 1.4 | 0.0156 | 0.43 | ( 0.22, 0.87) | 0.43 | ( 0.21, 0.87) | -0.02 | (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7615 |
| <75 | 500 | 20 | 4.0 | 500 | 8 | 1.6 | 0.0214 | 0.40 | ( 0.18, 0.90) | 0.39 | ( 0.17, 0.89) | -0.02 | (-0.04, 0.00) | |
| 75 to <85 | 427 | 13 | 3.0 | 417 | 5 | 1.2 | 0.0635 | 0.39 | ( 0.14, 1.09) | 0.39 | ( 0.14, 1.09) | -0.02 | (-0.04, 0.00) | |
| >=85 | 261 | 8 | 3.1 | 254 | 5 | 2.0 | 0.4277 | 0.64 | ( 0.21, 1.94) | 0.64 | ( 0.20, 1.97) | -0.01 | (-0.04, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.6561 |
| No | 1048 | 36 | 3.4 | 1031 | 15 | 1.5 | 0.0035 | 0.42 | ( 0.23, 0.77) | 0.42 | ( 0.23, 0.76) | -0.02 | (-0.03,-0.01) | |
| Yes | 140 | 5 | 3.6 | 140 | 3 | 2.1 | 0.4731 | 0.60 | ( 0.15, 2.46) | 0.59 | ( 0.14, 2.52) | -0.01 | (-0.05, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Glycosylated haemoglobin increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.3315 |
| <45 | 179 | 5 | 2.8 | 178 | 4 | 2.2 | 0.7421 | 0.80 ( 0.22, | 2.95) | 0.80 ( 0.21, | 3.03) | -0.01 (-0.04, 0.03) | |
| >=45 | 1009 | 36 | 3.6 | 993 | 14 | 1.4 | 0.0020 | 0.40 ( 0.21, | 0.73) | 0.39 ( 0.21, | 0.72) | -0.02 (-0.04,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.6083 |
| Normal (<30) | 250 | 7 | 2.8 | 257 | 5 | 1.9 | 0.5269 | 0.69 ( 0.22, | 2.16) | 0.69 ( 0.22, | 2.20) | -0.01 (-0.04, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 24 | 3.6 | 645 | 8 | 1.2 | 0.0063 | 0.35 ( 0.16, | 0.77) | 0.34 ( 0.15, | 0.76) | -0.02 (-0.04,-0.01) | |
| Macroalbuminuria (>300) | 260 | 10 | 3.8 | 261 | 5 | 1.9 | 0.1877 | 0.50 ( 0.17, | 1.44) | 0.49 ( 0.16, | 1.45) | -0.02 (-0.05, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.8259 |
| Low, moderate or high | 1018 | 35 | 3.4 | 1001 | 15 | 1.5 | 0.0050 | 0.44 ( 0.24, | 0.79) | 0.43 ( 0.23, | 0.79) | -0.02 (-0.03,-0.01) | |
| Very high | 167 | 6 | 3.6 | 162 | 3 | 1.9 | 0.3331 | 0.52 ( 0.13, | 2.03) | 0.51 ( 0.12, | 2.06) | -0.02 (-0.05, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.4621 |
| No | 205 | 10 | 4.9 | 211 | 3 | 1.4 | 0.0428 | 0.29 ( 0.08, | 1.04) | 0.28 ( 0.08, | 1.04) | -0.03 (-0.07, 0.00) | |
| Yes | 983 | 31 | 3.2 | 960 | 15 | 1.6 | 0.0211 | 0.50 ( 0.27, | 0.91) | 0.49 ( 0.26, | 0.91) | -0.02 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.9912 |
| No | 422 | 14 | 3.3 | 408 | 6 | 1.5 | 0.0828 | 0.44 ( 0.17, | 1.14) | 0.43 ( 0.17, | 1.14) | -0.02 (-0.04, 0.00) | |
| Yes | 766 | 27 | 3.5 | 763 | 12 | 1.6 | 0.0155 | 0.45 ( 0.23, | 0.87) | 0.44 ( 0.22, | 0.87) | -0.02 (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.4384 |
| No | 629 | 24 | 3.8 | 589 | 12 | 2.0 | 0.0671 | 0.53 ( 0.27, | 1.06) | 0.52 ( 0.26, | 1.06) | -0.02 (-0.04, 0.00) | |
| Yes | 559 | 17 | 3.0 | 582 | 6 | 1.0 | 0.0157 | 0.34 ( 0.13, | 0.85) | 0.33 ( 0.13, | 0.85) | -0.02 (-0.04, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Lipase increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 36 | 3.0 | 1171 | 35 | 3.0 | 0.9531 | 0.99 ( 0.62, 1.56) | 0.99 ( 0.61, 1.58) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Urine albumin/creatinine ratio increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 27 | 2.3 | 1171 | 18 | 1.5 | 0.1916 | 0.68 ( 0.37, 1.22) | 0.67 ( 0.37, 1.23) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood glucose increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 22 | 1.9 | 1171 | 13 | 1.1 | 0.1363 | 0.60 ( 0.30, | 1.18) | 0.59 ( 0.30, | 1.19) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Weight decreased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 19 | 1.6 | 0.4634 | 1.29 ( 0.66, 2.52) | 1.29 ( 0.65, 2.55) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood pressure increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 18 | 1.5 | 1171 | 18 | 1.5 | 0.9652 | 1.01 ( 0.53, 1.94) | 1.01 ( 0.53, 1.96) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood uric acid increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 18 | 1.5 | 1171 | 5 | 0.4 | 0.0072 | 0.28 | ( 0.10, 0.76) | 0.28 | ( 0.10, 0.75) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.3365 |
| Male | 864 | 13 | 1.5 | 837 | 5 | 0.6 | 0.0675 | 0.40 | ( 0.14, 1.11) | 0.39 | ( 0.14, 1.11) | -0.01 | (-0.02, 0.00) | |
| Female | 324 | 5 | 1.5 | 334 | 0 | 0 | 0.0368 | 0.09 | (<0.01, 1.59) | 0.09 | (<0.01, 1.58) | -0.02 | (-0.03, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.6583 |
| <65 | 569 | 9 | 1.6 | 547 | 3 | 0.5 | 0.0943 | 0.35 | ( 0.09, 1.27) | 0.34 | ( 0.09, 1.27) | -0.01 | (-0.02, 0.00) | |
| >=65 | 619 | 9 | 1.5 | 624 | 2 | 0.3 | 0.0329 | 0.22 | ( 0.05, 1.02) | 0.22 | ( 0.05, 1.01) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | |
| Europe | 468 | 4 | 0.9 | 434 | 1 | 0.2 | | | | | | | | |
| North America | 259 | 3 | 1.2 | 241 | 3 | 1.2 | | | | | | | | |
| Latin America | 177 | 3 | 1.7 | 191 | 1 | 0.5 | | | | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | | | | |
| Asia | 234 | 8 | 3.4 | 251 | 0 | 0 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1550 |
| <30 | 554 | 8 | 1.4 | 566 | 0 | 0 | 0.0067 | 0.06 | (<0.01, <1.00) | 0.06 | (<0.01, 0.99) | -0.01 | (-0.02, 0.00) | |
| >=30 | 634 | 10 | 1.6 | 605 | 5 | 0.8 | 0.2270 | 0.52 | ( 0.18, 1.52) | 0.52 | ( 0.18, 1.53) | -0.01 | (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7068 |
| <130 | 379 | 5 | 1.3 | 382 | 1 | 0.3 | 0.0991 | 0.20 | ( 0.02, 1.69) | 0.20 | ( 0.02, 1.69) | -0.01 | (-0.02, 0.00) | |
| >=130 | 809 | 13 | 1.6 | 789 | 4 | 0.5 | 0.0321 | 0.32 | ( 0.10, 0.96) | 0.31 | ( 0.10, 0.96) | -0.01 | (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3001 |
| <75 | 500 | 11 | 2.2 | 500 | 1 | 0.2 | 0.0037 | 0.09 | ( 0.01, 0.70) | 0.09 | ( 0.01, 0.69) | -0.02 | (-0.03,-0.01) | |
| 75 to <85 | 427 | 3 | 0.7 | 417 | 2 | 0.5 | 0.6730 | 0.68 | ( 0.11, 4.06) | 0.68 | ( 0.11, 4.10) | 0.00 | (-0.01, 0.01) | |
| >=85 | 261 | 4 | 1.5 | 254 | 2 | 0.8 | 0.4308 | 0.51 | ( 0.09, 2.78) | 0.51 | ( 0.09, 2.81) | -0.01 | (-0.03, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.4361 |
| No | 1048 | 14 | 1.3 | 1031 | 3 | 0.3 | 0.0082 | 0.22 | ( 0.06, 0.76) | 0.22 | ( 0.06, 0.75) | -0.01 | (-0.02, 0.00) | |
| Yes | 140 | 4 | 2.9 | 140 | 2 | 1.4 | 0.4092 | 0.50 | ( 0.09, 2.69) | 0.49 | ( 0.09, 2.73) | -0.01 | (-0.05, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood uric acid increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.4545 |
| <45 | 179 | 4 | 2.2 | 178 | 0 | 0 | 0.0726 | 0.11 (<0.01, 2.06) | 0.11 (<0.01, 2.04) | -0.02 (-0.05, 0.00) | |
| >=45 | 1009 | 14 | 1.4 | 993 | 5 | 0.5 | 0.0414 | 0.36 ( 0.13, >1.00) | 0.36 ( 0.13, 1.00) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.8958 |
| Normal (<30) | 250 | 4 | 1.6 | 257 | 1 | 0.4 | 0.1678 | 0.24 ( 0.03, 2.16) | 0.24 ( 0.03, 2.16) | -0.01 (-0.03, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 9 | 1.3 | 645 | 3 | 0.5 | 0.0966 | 0.35 ( 0.09, 1.28) | 0.35 ( 0.09, 1.28) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 260 | 5 | 1.9 | 261 | 1 | 0.4 | 0.0995 | 0.20 ( 0.02, 1.69) | 0.20 ( 0.02, 1.69) | -0.02 (-0.03, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.4636 |
| Low, moderate or high | 1018 | 14 | 1.4 | 1001 | 5 | 0.5 | 0.0416 | 0.36 ( 0.13, >1.00) | 0.36 ( 0.13, 1.00) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 4 | 2.4 | 162 | 0 | 0 | 0.0769 | 0.11 (<0.01, 2.11) | 0.11 (<0.01, 2.09) | -0.02 (-0.05, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.8940 |
| No | 205 | 3 | 1.5 | 211 | 1 | 0.5 | 0.3012 | 0.32 ( 0.03, 3.09) | 0.32 ( 0.03, 3.11) | -0.01 (-0.03, 0.01) | |
| Yes | 983 | 15 | 1.5 | 960 | 4 | 0.4 | 0.0130 | 0.27 ( 0.09, 0.82) | 0.27 ( 0.09, 0.82) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.5872 |
| No | 422 | 6 | 1.4 | 408 | 1 | 0.2 | 0.0638 | 0.17 ( 0.02, 1.43) | 0.17 ( 0.02, 1.42) | -0.01 (-0.02, 0.00) | |
| Yes | 766 | 12 | 1.6 | 763 | 4 | 0.5 | 0.0452 | 0.33 ( 0.11, 1.03) | 0.33 ( 0.11, 1.03) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.9407 |
| No | 629 | 8 | 1.3 | 589 | 2 | 0.3 | 0.0716 | 0.27 ( 0.06, 1.25) | 0.26 ( 0.06, 1.25) | -0.01 (-0.02, 0.00) | |
| Yes | 559 | 10 | 1.8 | 582 | 3 | 0.5 | 0.0428 | 0.29 ( 0.08, 1.04) | 0.28 ( 0.08, 1.04) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Glomerular filtration rate decreased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 17 | 1.5 | 0.6913 | 1.15 ( 0.58, 2.29) | 1.15 ( 0.57, 2.32) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood potassium increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 16 | 1.3 | 1171 | 7 | 0.6 | 0.0641 | 0.44 ( 0.18, 1.07) | 0.44 ( 0.18, 1.07) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood triglycerides increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 9 | 0.8 | 1171 | 15 | 1.3 | 0.2053 | 1.69 ( 0.74, 3.85) | 1.70 ( 0.74, 3.90) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood urea increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 12 | 1.0 | 0.5871 | 0.81 ( 0.38, 1.73) | 0.81 ( 0.38, 1.74) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Blood magnesium decreased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 7 | 0.6 | 0.2626 | 0.59 ( 0.23, 1.50) | 0.59 ( 0.23, 1.50) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Oedema peripheral

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 110 | 9.3 | 1171 | 59 | 5.0 | <0.0001 | 0.54 | ( 0.40, 0.74) | 0.52 | ( 0.37, 0.72) | -0.04 | (-0.06,-0.02) | |
| Sex | | | | | | | | | | | | | | 0.1652 |
| Male | 864 | 78 | 9.0 | 837 | 35 | 4.2 | <0.0001 | 0.46 | ( 0.31, 0.68) | 0.44 | ( 0.29, 0.66) | -0.05 | (-0.07,-0.03) | |
| Female | 324 | 32 | 9.9 | 334 | 24 | 7.2 | 0.2162 | 0.73 | ( 0.44, 1.21) | 0.71 | ( 0.41, 1.23) | -0.03 | (-0.07, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.8461 |
| <65 | 569 | 35 | 6.2 | 547 | 19 | 3.5 | 0.0372 | 0.56 | ( 0.33, 0.97) | 0.55 | ( 0.31, 0.97) | -0.03 | (-0.05, 0.00) | |
| >=65 | 619 | 75 | 12.1 | 624 | 40 | 6.4 | 0.0005 | 0.53 | ( 0.37, 0.76) | 0.50 | ( 0.33, 0.74) | -0.06 | (-0.09,-0.02) | |
| Region | | | | | | | | | | | | | | 0.4005 |
| Europe | 468 | 36 | 7.7 | 434 | 18 | 4.1 | 0.0249 | 0.54 | ( 0.31, 0.93) | 0.52 | ( 0.29, 0.93) | -0.04 | (-0.07, 0.00) | |
| North America | 259 | 32 | 12.4 | 241 | 12 | 5.0 | 0.0036 | 0.40 | ( 0.21, 0.76) | 0.37 | ( 0.19, 0.74) | -0.07 | (-0.12,-0.03) | |
| Latin America | 177 | 19 | 10.7 | 191 | 8 | 4.2 | 0.0161 | 0.39 | ( 0.18, 0.87) | 0.36 | ( 0.15, 0.85) | -0.07 | (-0.12,-0.01) | |
| Africa | 50 | 3 | 6.0 | 54 | 2 | 3.7 | 0.5844 | 0.62 | ( 0.11, 3.54) | 0.60 | ( 0.10, 3.76) | -0.02 | (-0.11, 0.06) | |
| Asia | 234 | 20 | 8.5 | 251 | 19 | 7.6 | 0.6925 | 0.89 | ( 0.49, 1.62) | 0.88 | ( 0.46, 1.69) | -0.01 | (-0.06, 0.04) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0752 |
| <30 | 554 | 39 | 7.0 | 566 | 30 | 5.3 | 0.2261 | 0.75 | ( 0.47, 1.19) | 0.74 | ( 0.45, 1.21) | -0.02 | (-0.05, 0.01) | |
| >=30 | 634 | 71 | 11.2 | 605 | 29 | 4.8 | <0.0001 | 0.43 | ( 0.28, 0.65) | 0.40 | ( 0.26, 0.62) | -0.06 | (-0.09,-0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0890 |
| <130 | 379 | 37 | 9.8 | 382 | 13 | 3.4 | 0.0004 | 0.35 | ( 0.19, 0.65) | 0.33 | ( 0.17, 0.62) | -0.06 | (-0.10,-0.03) | |
| >=130 | 809 | 73 | 9.0 | 789 | 46 | 5.8 | 0.0151 | 0.65 | ( 0.45, 0.92) | 0.62 | ( 0.43, 0.92) | -0.03 | (-0.06,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2107 |
| <75 | 500 | 58 | 11.6 | 500 | 24 | 4.8 | <0.0001 | 0.41 | ( 0.26, 0.65) | 0.38 | ( 0.23, 0.63) | -0.07 | (-0.10,-0.03) | |
| 75 to <85 | 427 | 32 | 7.5 | 417 | 24 | 5.8 | 0.3103 | 0.77 | ( 0.46, 1.28) | 0.75 | ( 0.44, 1.30) | -0.02 | (-0.05, 0.02) | |
| >=85 | 261 | 20 | 7.7 | 254 | 11 | 4.3 | 0.1119 | 0.57 | ( 0.28, 1.16) | 0.55 | ( 0.26, 1.16) | -0.03 | (-0.07, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.0166 |
| No | 1048 | 91 | 8.7 | 1031 | 57 | 5.5 | 0.0052 | 0.64 | ( 0.46, 0.88) | 0.62 | ( 0.44, 0.87) | -0.03 | (-0.05,-0.01) | |
| Yes | 140 | 19 | 13.6 | 140 | 2 | 1.4 | 0.0001 | 0.11 | ( 0.02, 0.44) | 0.09 | ( 0.02, 0.40) | -0.12 | (-0.18,-0.06) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Oedema peripheral

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.5007 |
| <45 | 179 | 23 | 12.8 | 178 | 15 | 8.4 | 0.1755 | 0.66 ( 0.35, | 1.21) | 0.62 ( 0.31, | 1.24) | -0.04 (-0.11, 0.02) | |
| >=45 | 1009 | 87 | 8.6 | 993 | 44 | 4.4 | 0.0001 | 0.51 ( 0.36, | 0.73) | 0.49 ( 0.34, | 0.71) | -0.04 (-0.06,-0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.1282 |
| Normal (<30) | 250 | 20 | 8.0 | 257 | 13 | 5.1 | 0.1795 | 0.63 ( 0.32, | 1.24) | 0.61 ( 0.30, | 1.26) | -0.03 (-0.07, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 64 | 9.5 | 645 | 24 | 3.7 | <0.0001 | 0.39 ( 0.25, | 0.62) | 0.37 ( 0.23, | 0.60) | -0.06 (-0.08,-0.03) | |
| Macroalbuminuria (>300) | 260 | 26 | 10.0 | 261 | 21 | 8.0 | 0.4363 | 0.80 ( 0.46, | 1.39) | 0.79 ( 0.43, | 1.44) | -0.02 (-0.07, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.2880 |
| Low, moderate or high | 1018 | 87 | 8.5 | 1001 | 42 | 4.2 | <0.0001 | 0.49 ( 0.34, | 0.70) | 0.47 ( 0.32, | 0.68) | -0.04 (-0.06,-0.02) | |
| Very high | 167 | 23 | 13.8 | 162 | 16 | 9.9 | 0.2744 | 0.72 ( 0.39, | 1.31) | 0.69 ( 0.35, | 1.35) | -0.04 (-0.11, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.1919 |
| No | 205 | 12 | 5.9 | 211 | 11 | 5.2 | 0.7751 | 0.89 ( 0.40, | 1.97) | 0.88 ( 0.38, | 2.05) | -0.01 (-0.05, 0.04) | |
| Yes | 983 | 98 | 10.0 | 960 | 48 | 5.0 | <0.0001 | 0.50 ( 0.36, | 0.70) | 0.48 ( 0.33, | 0.68) | -0.05 (-0.07,-0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.9742 |
| No | 422 | 34 | 8.1 | 408 | 18 | 4.4 | 0.0303 | 0.55 ( 0.31, | 0.95) | 0.53 ( 0.29, | 0.95) | -0.04 (-0.07, 0.00) | |
| Yes | 766 | 76 | 9.9 | 763 | 41 | 5.4 | 0.0008 | 0.54 ( 0.38, | 0.78) | 0.52 ( 0.35, | 0.76) | -0.05 (-0.07,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.6630 |
| No | 629 | 42 | 6.7 | 589 | 23 | 3.9 | 0.0315 | 0.58 ( 0.36, | 0.96) | 0.57 ( 0.34, | 0.96) | -0.03 (-0.05, 0.00) | |
| Yes | 559 | 68 | 12.2 | 582 | 36 | 6.2 | 0.0005 | 0.51 ( 0.35, | 0.75) | 0.48 ( 0.31, | 0.73) | -0.06 (-0.09,-0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Chest pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 50 | 4.2 | 1171 | 57 | 4.9 | 0.4419 | 1.16 ( 0.80, | 1.68) | 1.16 ( 0.79, | 1.72) | 0.01 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Fatigue

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 37 | 3.1 | 1171 | 25 | 2.1 | 0.1370 | 0.69 ( 0.42, 1.13) | 0.68 ( 0.41, 1.13) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Asthenia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 29 | 2.4 | 1171 | 25 | 2.1 | 0.6191 | 0.87 ( 0.52, 1.48) | 0.87 ( 0.51, 1.50) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Pyrexia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 24 | 2.0 | 1171 | 28 | 2.4 | 0.5396 | 1.18 ( 0.69, 2.03) | 1.19 ( 0.68, 2.06) | 0.00 (-0.01, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Oedema

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 22 | 1.9 | 1171 | 7 | 0.6 | 0.0057 | 0.32 ( 0.14, | 0.75) | 0.32 ( 0.14, | 0.75) | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | 0.8112 |
| Male | 864 | 14 | 1.6 | 837 | 4 | 0.5 | 0.0213 | 0.29 ( 0.10, | 0.89) | 0.29 ( 0.10, | 0.89) | -0.01 (-0.02, 0.00) | |
| Female | 324 | 8 | 2.5 | 334 | 3 | 0.9 | 0.1161 | 0.36 ( 0.10, | 1.36) | 0.36 ( 0.09, | 1.36) | -0.02 (-0.04, 0.00) | |
| Age [years] | | | | | | | | | | | | | 0.1346 |
| <65 | 569 | 9 | 1.6 | 547 | 0 | 0 | 0.0052 | 0.05 (<0.01, | 0.94) | 0.05 (<0.01, | 0.93) | -0.02 (-0.03, 0.00) | |
| >=65 | 619 | 13 | 2.1 | 624 | 7 | 1.1 | 0.1705 | 0.53 ( 0.21, | 1.33) | 0.53 ( 0.21, | 1.33) | -0.01 (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | 0.9986 |
| Europe | 468 | 4 | 0.9 | 434 | 1 | 0.2 | 0.2070 | 0.27 ( 0.03, | 2.40) | 0.27 ( 0.03, | 2.41) | -0.01 (-0.02, 0.00) | |
| North America | 259 | 11 | 4.2 | 241 | 4 | 1.7 | 0.0901 | 0.39 ( 0.13, | 1.21) | 0.38 ( 0.12, | 1.21) | -0.03 (-0.06, 0.00) | |
| Latin America | 177 | 1 | 0.6 | 191 | 0 | 0 | 0.4453 | 0.31 ( 0.01, | 7.54) | 0.31 ( 0.01, | 7.59) | -0.01 (-0.02, 0.01) | |
| Africa | 50 | 1 | 2.0 | 54 | 0 | 0 | 0.4423 | 0.31 ( 0.01, | 7.42) | 0.30 ( 0.01, | 7.61) | -0.02 (-0.07, 0.03) | |
| Asia | 234 | 5 | 2.1 | 251 | 2 | 0.8 | 0.2163 | 0.37 ( 0.07, | 1.90) | 0.37 ( 0.07, | 1.91) | -0.01 (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.9892 |
| <30 | 554 | 9 | 1.6 | 566 | 3 | 0.5 | 0.0753 | 0.33 ( 0.09, | 1.20) | 0.32 ( 0.09, | 1.20) | -0.01 (-0.02, 0.00) | |
| >=30 | 634 | 13 | 2.1 | 605 | 4 | 0.7 | 0.0356 | 0.32 ( 0.11, | 0.98) | 0.32 ( 0.10, | 0.98) | -0.01 (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.2074 |
| <130 | 379 | 4 | 1.1 | 382 | 3 | 0.8 | 0.6964 | 0.74 ( 0.17, | 3.30) | 0.74 ( 0.16, | 3.34) | 0.00 (-0.02, 0.01) | |
| >=130 | 809 | 18 | 2.2 | 789 | 4 | 0.5 | 0.0032 | 0.23 ( 0.08, | 0.67) | 0.22 ( 0.08, | 0.66) | -0.02 (-0.03,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.9689 |
| <75 | 500 | 13 | 2.6 | 500 | 4 | 0.8 | 0.0277 | 0.31 ( 0.10, | 0.94) | 0.30 ( 0.10, | 0.93) | -0.02 (-0.03, 0.00) | |
| 75 to <85 | 427 | 8 | 1.9 | 417 | 3 | 0.7 | 0.1394 | 0.38 ( 0.10, | 1.44) | 0.38 ( 0.10, | 1.44) | -0.01 (-0.03, 0.00) | |
| >=85 | 261 | 1 | 0.4 | 254 | 0 | 0 | 0.4906 | 0.34 ( 0.01, | 8.37) | 0.34 ( 0.01, | 8.41) | 0.00 (-0.01, 0.01) | |
| History of heart failure | | | | | | | | | | | | | 0.9757 |
| No | 1048 | 19 | 1.8 | 1031 | 6 | 0.6 | 0.0100 | 0.32 ( 0.13, | 0.80) | 0.32 ( 0.13, | 0.80) | -0.01 (-0.02, 0.00) | |
| Yes | 140 | 3 | 2.1 | 140 | 1 | 0.7 | 0.3138 | 0.33 ( 0.04, | 3.17) | 0.33 ( 0.03, | 3.20) | -0.01 (-0.04, 0.01) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Oedema

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.7600 |
| <45 | 179 | 5 | 2.8 | 178 | 2 | 1.1 | 0.2552 | 0.40 ( 0.08, | 2.05) | 0.40 ( 0.08, | 2.07) | -0.02 (-0.05, 0.01) | |
| >=45 | 1009 | 17 | 1.7 | 993 | 5 | 0.5 | 0.0112 | 0.30 ( 0.11, | 0.81) | 0.30 ( 0.11, | 0.80) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.0938 |
| Normal (<30) | 250 | 3 | 1.2 | 257 | 4 | 1.6 | 0.7310 | 1.30 ( 0.29, | 5.74) | 1.30 ( 0.29, | 5.88) | 0.00 (-0.02, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 12 | 1.8 | 645 | 1 | 0.2 | 0.0028 | 0.09 ( 0.01, | 0.67) | 0.09 ( 0.01, | 0.66) | -0.02 (-0.03,-0.01) | |
| Macroalbuminuria (>300) | 260 | 7 | 2.7 | 261 | 2 | 0.8 | 0.0916 | 0.28 ( 0.06, | 1.36) | 0.28 ( 0.06, | 1.36) | -0.02 (-0.04, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.2054 |
| Low, moderate or high | 1018 | 15 | 1.5 | 1001 | 7 | 0.7 | 0.0939 | 0.47 ( 0.19, | 1.16) | 0.47 ( 0.19, | 1.16) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 7 | 4.2 | 162 | 0 | 0 | 0.0138 | 0.07 (<0.01, | 1.19) | 0.07 (<0.01, | 1.16) | -0.04 (-0.07,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.0639 |
| No | 205 | 2 | 1.0 | 211 | 3 | 1.4 | 0.6763 | 1.46 ( 0.25, | 8.63) | 1.46 ( 0.24, | 8.85) | 0.00 (-0.02, 0.03) | |
| Yes | 983 | 20 | 2.0 | 960 | 4 | 0.4 | 0.0012 | 0.20 ( 0.07, | 0.60) | 0.20 ( 0.07, | 0.59) | -0.02 (-0.03,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.5694 |
| No | 422 | 7 | 1.7 | 408 | 3 | 0.7 | 0.2228 | 0.44 ( 0.12, | 1.70) | 0.44 ( 0.11, | 1.71) | -0.01 (-0.02, 0.01) | |
| Yes | 766 | 15 | 2.0 | 763 | 4 | 0.5 | 0.0114 | 0.27 ( 0.09, | 0.80) | 0.26 ( 0.09, | 0.80) | -0.01 (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.9596 |
| No | 629 | 7 | 1.1 | 589 | 2 | 0.3 | 0.1153 | 0.31 ( 0.06, | 1.46) | 0.30 ( 0.06, | 1.46) | -0.01 (-0.02, 0.00) | |
| Yes | 559 | 15 | 2.7 | 582 | 5 | 0.9 | 0.0189 | 0.32 ( 0.12, | 0.88) | 0.31 ( 0.11, | 0.87) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 20 | 1.7 | 1171 | 12 | 1.0 | 0.1667 | 0.61 ( 0.30, 1.24) | 0.60 ( 0.29, 1.24) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Peripheral swelling

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 20 | 1.7 | 1171 | 9 | 0.8 | 0.0438 | 0.46 ( 0.21, <1.00) | 0.45 ( 0.21, 1.00) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | 0.9415 |
| Male | 864 | 16 | 1.9 | 837 | 7 | 0.8 | 0.0698 | 0.45 ( 0.19, 1.09) | 0.45 ( 0.18, 1.09) | -0.01 | (-0.02, 0.00) | |
| Female | 324 | 4 | 1.2 | 334 | 2 | 0.6 | 0.3910 | 0.49 ( 0.09, 2.63) | 0.48 ( 0.09, 2.65) | -0.01 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | 0.5574 |
| <65 | 569 | 9 | 1.6 | 547 | 5 | 0.9 | 0.3164 | 0.58 ( 0.19, 1.71) | 0.57 ( 0.19, 1.72) | -0.01 | (-0.02, 0.01) | |
| >=65 | 619 | 11 | 1.8 | 624 | 4 | 0.6 | 0.0666 | 0.36 ( 0.12, 1.13) | 0.36 ( 0.11, 1.13) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | 0.2473 |
| Europe | 468 | 6 | 1.3 | 434 | 0 | 0 | 0.0294 | 0.08 (<0.01, 1.47) | 0.08 (<0.01, 1.46) | -0.01 | (-0.02, 0.00) | |
| North America | 259 | 4 | 1.5 | 241 | 6 | 2.5 | 0.4506 | 1.61 ( 0.46, 5.64) | 1.63 ( 0.45, 5.84) | 0.01 | (-0.02, 0.03) | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | 0.9698 | 0.93 ( 0.02, 46.47) | 0.93 ( 0.02, 46.96) | 0.00 | (-0.01, 0.01) | |
| Africa | 50 | 1 | 2.0 | 54 | 0 | 0 | 0.4423 | 0.31 ( 0.01, 7.42) | 0.30 ( 0.01, 7.61) | -0.02 | (-0.07, 0.03) | |
| Asia | 234 | 9 | 3.8 | 251 | 3 | 1.2 | 0.0604 | 0.31 ( 0.09, 1.13) | 0.30 ( 0.08, 1.13) | -0.03 | (-0.05, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0101 |
| <30 | 554 | 14 | 2.5 | 566 | 1 | 0.2 | 0.0006 | 0.07 (<0.01, 0.53) | 0.07 (<0.01, 0.52) | -0.02 | (-0.04,-0.01) | |
| >=30 | 634 | 6 | 0.9 | 605 | 8 | 1.3 | 0.5314 | 1.40 ( 0.49, 4.00) | 1.40 ( 0.48, 4.07) | 0.00 | (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0225 |
| <130 | 379 | 4 | 1.1 | 382 | 6 | 1.6 | 0.5326 | 1.49 ( 0.42, 5.23) | 1.50 ( 0.42, 5.34) | 0.01 | (-0.01, 0.02) | |
| >=130 | 809 | 16 | 2.0 | 789 | 3 | 0.4 | 0.0032 | 0.19 ( 0.06, 0.66) | 0.19 ( 0.05, 0.65) | -0.02 | (-0.03,-0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.1968 |
| <75 | 500 | 9 | 1.8 | 500 | 7 | 1.4 | 0.6142 | 0.78 ( 0.29, 2.07) | 0.77 ( 0.29, 2.10) | 0.00 | (-0.02, 0.01) | |
| 75 to <85 | 427 | 10 | 2.3 | 417 | 1 | 0.2 | 0.0071 | 0.10 ( 0.01, 0.80) | 0.10 ( 0.01, 0.79) | -0.02 | (-0.04,-0.01) | |
| >=85 | 261 | 1 | 0.4 | 254 | 1 | 0.4 | 0.9846 | 1.03 ( 0.06, 16.34) | 1.03 ( 0.06, 16.52) | 0.00 | (-0.01, 0.01) | |
| History of heart failure | | | | | | | | | | | | 0.3933 |
| No | 1048 | 18 | 1.7 | 1031 | 7 | 0.7 | 0.0298 | 0.40 ( 0.17, 0.94) | 0.39 ( 0.16, 0.94) | -0.01 | (-0.02, 0.00) | |
| Yes | 140 | 2 | 1.4 | 140 | 2 | 1.4 | 1.0000 | 1.00 ( 0.14, 7.00) | 1.00 ( 0.14, 7.20) | 0.00 | (-0.03, 0.03) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Peripheral swelling

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.3985 |
| <45 | 179 | 5 | 2.8 | 178 | 1 | 0.6 | 0.1010 | 0.20 ( 0.02, | 1.70) | 0.20 ( 0.02, | 1.70) | -0.02 (-0.05, 0.00) | |
| >=45 | 1009 | 15 | 1.5 | 993 | 8 | 0.8 | 0.1528 | 0.54 ( 0.23, | 1.27) | 0.54 ( 0.23, | 1.28) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.6631 |
| Normal (<30) | 250 | 2 | 0.8 | 257 | 1 | 0.4 | 0.5464 | 0.49 ( 0.04, | 5.33) | 0.48 ( 0.04, | 5.38) | 0.00 (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 8 | 1.2 | 645 | 5 | 0.8 | 0.4508 | 0.65 ( 0.22, | 1.99) | 0.65 ( 0.21, | 2.00) | 0.00 (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 260 | 10 | 3.8 | 261 | 3 | 1.1 | 0.0485 | 0.30 ( 0.08, | 1.07) | 0.29 ( 0.08, | 1.07) | -0.03 (-0.05, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.1483 |
| Low, moderate or high | 1018 | 12 | 1.2 | 1001 | 8 | 0.8 | 0.3892 | 0.68 ( 0.28, | 1.65) | 0.68 ( 0.27, | 1.66) | 0.00 (-0.01, 0.00) | |
| Very high | 167 | 8 | 4.8 | 162 | 1 | 0.6 | 0.0203 | 0.13 ( 0.02, | 1.02) | 0.12 ( 0.02, | 1.00) | -0.04 (-0.08,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.3790 |
| No | 205 | 5 | 2.4 | 211 | 1 | 0.5 | 0.0928 | 0.19 ( 0.02, | 1.65) | 0.19 ( 0.02, | 1.64) | -0.02 (-0.04, 0.00) | |
| Yes | 983 | 15 | 1.5 | 960 | 8 | 0.8 | 0.1582 | 0.55 ( 0.23, | 1.28) | 0.54 ( 0.23, | 1.29) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.0742 |
| No | 422 | 10 | 2.4 | 408 | 1 | 0.2 | 0.0075 | 0.10 ( 0.01, | 0.80) | 0.10 ( 0.01, | 0.79) | -0.02 (-0.04,-0.01) | |
| Yes | 766 | 10 | 1.3 | 763 | 8 | 1.0 | 0.6413 | 0.80 ( 0.32, | 2.02) | 0.80 ( 0.31, | 2.04) | 0.00 (-0.01, 0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.1411 |
| No | 629 | 11 | 1.7 | 589 | 2 | 0.3 | 0.0168 | 0.19 ( 0.04, | 0.87) | 0.19 ( 0.04, | 0.87) | -0.01 (-0.03, 0.00) | |
| Yes | 559 | 9 | 1.6 | 582 | 7 | 1.2 | 0.5586 | 0.75 ( 0.28, | 1.99) | 0.74 ( 0.28, | 2.01) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Chest discomfort

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 18 | 1.5 | 1171 | 15 | 1.3 | 0.6282 | 0.85 ( 0.43, 1.67) | 0.84 ( 0.42, 1.68) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Malaise

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 8 | 0.7 | 1171 | 14 | 1.2 | 0.1871 | 1.78 ( 0.75, 4.22) | 1.78 ( 0.75, 4.27) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypertension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 145 | 12.2 | 1171 | 109 | 9.3 | 0.0232 | 0.76 | ( 0.60, 0.96) | 0.74 | ( 0.57, 0.96) | -0.03 | (-0.05, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.2813 |
| Male | 864 | 105 | 12.2 | 837 | 71 | 8.5 | 0.0130 | 0.70 | ( 0.52, 0.93) | 0.67 | ( 0.49, 0.92) | -0.04 | (-0.07,-0.01) | |
| Female | 324 | 40 | 12.3 | 334 | 38 | 11.4 | 0.7008 | 0.92 | ( 0.61, 1.40) | 0.91 | ( 0.57, 1.46) | -0.01 | (-0.06, 0.04) | |
| Age [years] | | | | | | | | | | | | | | 0.4142 |
| <65 | 569 | 74 | 13.0 | 547 | 49 | 9.0 | 0.0309 | 0.69 | ( 0.49, 0.97) | 0.66 | ( 0.45, 0.96) | -0.04 | (-0.08, 0.00) | |
| >=65 | 619 | 71 | 11.5 | 624 | 60 | 9.6 | 0.2870 | 0.84 | ( 0.61, 1.16) | 0.82 | ( 0.57, 1.18) | -0.02 | (-0.05, 0.02) | |
| Region | | | | | | | | | | | | | | 0.6860 |
| Europe | 468 | 55 | 11.8 | 434 | 33 | 7.6 | 0.0359 | 0.65 | ( 0.43, 0.98) | 0.62 | ( 0.39, 0.97) | -0.04 | (-0.08, 0.00) | |
| North America | 259 | 23 | 8.9 | 241 | 15 | 6.2 | 0.2627 | 0.70 | ( 0.37, 1.31) | 0.68 | ( 0.35, 1.34) | -0.03 | (-0.07, 0.02) | |
| Latin America | 177 | 30 | 16.9 | 191 | 26 | 13.6 | 0.3733 | 0.80 | ( 0.50, 1.30) | 0.77 | ( 0.44, 1.37) | -0.03 | (-0.11, 0.04) | |
| Africa | 50 | 5 | 10.0 | 54 | 8 | 14.8 | 0.4582 | 1.48 | ( 0.52, 4.23) | 1.57 | ( 0.48, 5.15) | 0.05 | (-0.08, 0.17) | |
| Asia | 234 | 32 | 13.7 | 251 | 27 | 10.8 | 0.3259 | 0.79 | ( 0.49, 1.27) | 0.76 | ( 0.44, 1.31) | -0.03 | (-0.09, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6970 |
| <30 | 554 | 78 | 14.1 | 566 | 63 | 11.1 | 0.1369 | 0.79 | ( 0.58, 1.08) | 0.76 | ( 0.54, 1.09) | -0.03 | (-0.07, 0.01) | |
| >=30 | 634 | 67 | 10.6 | 605 | 46 | 7.6 | 0.0700 | 0.72 | ( 0.50, 1.03) | 0.70 | ( 0.47, 1.03) | -0.03 | (-0.06, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7163 |
| <130 | 379 | 23 | 6.1 | 382 | 16 | 4.2 | 0.2396 | 0.69 | ( 0.37, 1.29) | 0.68 | ( 0.35, 1.30) | -0.02 | (-0.05, 0.01) | |
| >=130 | 809 | 122 | 15.1 | 789 | 93 | 11.8 | 0.0537 | 0.78 | ( 0.61, >1.00) | 0.75 | ( 0.56, 1.01) | -0.03 | (-0.07, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8939 |
| <75 | 500 | 48 | 9.6 | 500 | 35 | 7.0 | 0.1362 | 0.73 | ( 0.48, 1.11) | 0.71 | ( 0.45, 1.12) | -0.03 | (-0.06, 0.01) | |
| 75 to <85 | 427 | 47 | 11.0 | 417 | 38 | 9.1 | 0.3606 | 0.83 | ( 0.55, 1.24) | 0.81 | ( 0.52, 1.27) | -0.02 | (-0.06, 0.02) | |
| >=85 | 261 | 50 | 19.2 | 254 | 36 | 14.2 | 0.1295 | 0.74 | ( 0.50, 1.09) | 0.70 | ( 0.44, 1.11) | -0.05 | (-0.11, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.5169 |
| No | 1048 | 127 | 12.1 | 1031 | 98 | 9.5 | 0.0552 | 0.78 | ( 0.61, 1.01) | 0.76 | ( 0.58, 1.01) | -0.03 | (-0.05, 0.00) | |
| Yes | 140 | 18 | 12.9 | 140 | 11 | 7.9 | 0.1698 | 0.61 | ( 0.30, 1.25) | 0.58 | ( 0.26, 1.27) | -0.05 | (-0.12, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypertension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.2658 |
| <45 | 179 | 21 | 11.7 | 178 | 11 | 6.2 | 0.0663 | 0.53 ( 0.26, | 1.06) | 0.50 ( 0.23, | 1.06) | -0.06 (-0.11, 0.00) | |
| >=45 | 1009 | 124 | 12.3 | 993 | 98 | 9.9 | 0.0846 | 0.80 ( 0.63, | 1.03) | 0.78 ( 0.59, | 1.03) | -0.02 (-0.05, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.9579 |
| Normal (<30) | 250 | 19 | 7.6 | 257 | 14 | 5.4 | 0.3260 | 0.72 ( 0.37, | 1.40) | 0.70 ( 0.34, | 1.43) | -0.02 (-0.06, 0.02) | |
| Microalbuminuria (30 to <=300) | 675 | 77 | 11.4 | 645 | 55 | 8.5 | 0.0812 | 0.75 ( 0.54, | 1.04) | 0.72 ( 0.50, | 1.04) | -0.03 (-0.06, 0.00) | |
| Macroalbuminuria (>300) | 260 | 49 | 18.8 | 261 | 39 | 14.9 | 0.2344 | 0.79 ( 0.54, | 1.16) | 0.76 ( 0.48, | 1.20) | -0.04 (-0.10, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.9035 |
| Low, moderate or high | 1018 | 120 | 11.8 | 1001 | 89 | 8.9 | 0.0327 | 0.75 ( 0.58, | 0.98) | 0.73 ( 0.55, | 0.98) | -0.03 (-0.06, 0.00) | |
| Very high | 167 | 25 | 15.0 | 162 | 19 | 11.7 | 0.3878 | 0.78 ( 0.45, | 1.37) | 0.75 ( 0.40, | 1.43) | -0.03 (-0.11, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.6616 |
| No | 205 | 19 | 9.3 | 211 | 17 | 8.1 | 0.6604 | 0.87 ( 0.47, | 1.62) | 0.86 ( 0.43, | 1.70) | -0.01 (-0.07, 0.04) | |
| Yes | 983 | 126 | 12.8 | 960 | 92 | 9.6 | 0.0239 | 0.75 ( 0.58, | 0.96) | 0.72 ( 0.54, | 0.96) | -0.03 (-0.06, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.5160 |
| No | 422 | 62 | 14.7 | 408 | 50 | 12.3 | 0.3043 | 0.83 ( 0.59, | 1.18) | 0.81 ( 0.54, | 1.21) | -0.02 (-0.07, 0.02) | |
| Yes | 766 | 83 | 10.8 | 763 | 59 | 7.7 | 0.0366 | 0.71 ( 0.52, | 0.98) | 0.69 ( 0.49, | 0.98) | -0.03 (-0.06, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.7240 |
| No | 629 | 84 | 13.4 | 589 | 58 | 9.8 | 0.0566 | 0.74 ( 0.54, | 1.01) | 0.71 ( 0.50, | 1.01) | -0.04 (-0.07, 0.00) | |
| Yes | 559 | 61 | 10.9 | 582 | 51 | 8.8 | 0.2225 | 0.80 ( 0.56, | 1.14) | 0.78 ( 0.53, | 1.16) | -0.02 (-0.06, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 39 | 3.3 | 1171 | 31 | 2.6 | 0.3631 | 0.81 ( 0.51, | 1.28) | 0.80 ( 0.50, | 1.29) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Peripheral arterial occlusive disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 24 | 2.0 | 1171 | 27 | 2.3 | 0.6335 | 1.14 ( 0.66, 1.97) | 1.14 ( 0.66, 2.00) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Peripheral vascular disorder

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 8 | 0.7 | 0.2879 | 0.62 ( 0.26, 1.50) | 0.62 ( 0.26, 1.51) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Orthostatic hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 6 | 0.5 | 1171 | 12 | 1.0 | 0.1470 | 2.03 ( 0.76, 5.39) | 2.04 ( 0.76, 5.45) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Haematoma

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 8 | 0.7 | 0.3865 | 0.68 ( 0.28, 1.65) | 0.67 ( 0.27, 1.66) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Cough

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 80 | 6.7 | 1171 | 71 | 6.1 | 0.5057 | 0.90 ( 0.66, | 1.23) | 0.89 ( 0.64, | 1.24) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Dyspnoea

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 68 | 5.7 | 1171 | 35 | 3.0 | 0.0012 | 0.52 ( 0.35, 0.78) | 0.51 ( 0.33, 0.77) | -0.03 (-0.04,-0.01) | |
| Sex | | | | | | | | | | | 0.4867 |
| Male | 864 | 49 | 5.7 | 837 | 27 | 3.2 | 0.0147 | 0.57 ( 0.36, 0.90) | 0.55 ( 0.34, 0.90) | -0.02 (-0.04, 0.00) | |
| Female | 324 | 19 | 5.9 | 334 | 8 | 2.4 | 0.0249 | 0.41 ( 0.18, 0.92) | 0.39 ( 0.17, 0.91) | -0.03 (-0.07, 0.00) | |
| Age [years] | | | | | | | | | | | 0.1257 |
| <65 | 569 | 18 | 3.2 | 547 | 14 | 2.6 | 0.5456 | 0.81 ( 0.41, 1.61) | 0.80 ( 0.40, 1.63) | -0.01 (-0.03, 0.01) | |
| >=65 | 619 | 50 | 8.1 | 624 | 21 | 3.4 | 0.0003 | 0.42 ( 0.25, 0.69) | 0.40 ( 0.24, 0.67) | -0.05 (-0.07,-0.02) | |
| Region | | | | | | | | | | | 0.6830 |
| Europe | 468 | 24 | 5.1 | 434 | 16 | 3.7 | 0.2933 | 0.72 ( 0.39, 1.33) | 0.71 ( 0.37, 1.35) | -0.01 (-0.04, 0.01) | |
| North America | 259 | 28 | 10.8 | 241 | 14 | 5.8 | 0.0439 | 0.54 ( 0.29, <1.00) | 0.51 ( 0.26, 0.99) | -0.05 (-0.10, 0.00) | |
| Latin America | 177 | 7 | 4.0 | 191 | 2 | 1.0 | 0.0712 | 0.26 ( 0.06, 1.26) | 0.26 ( 0.05, 1.25) | -0.03 (-0.06, 0.00) | |
| Africa | 50 | 2 | 4.0 | 54 | 0 | 0 | 0.2155 | 0.19 (<0.01, 3.77) | 0.18 (<0.01, 3.80) | -0.04 (-0.10, 0.02) | |
| Asia | 234 | 7 | 3.0 | 251 | 3 | 1.2 | 0.1642 | 0.40 ( 0.10, 1.53) | 0.39 ( 0.10, 1.54) | -0.02 (-0.04, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.0480 |
| <30 | 554 | 32 | 5.8 | 566 | 10 | 1.8 | 0.0004 | 0.31 ( 0.15, 0.62) | 0.29 ( 0.14, 0.60) | -0.04 (-0.06,-0.02) | |
| >=30 | 634 | 36 | 5.7 | 605 | 25 | 4.1 | 0.2087 | 0.73 ( 0.44, 1.20) | 0.72 ( 0.42, 1.21) | -0.02 (-0.04, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.5324 |
| <130 | 379 | 25 | 6.6 | 382 | 11 | 2.9 | 0.0157 | 0.44 ( 0.22, 0.87) | 0.42 ( 0.20, 0.87) | -0.04 (-0.07,-0.01) | |
| >=130 | 809 | 43 | 5.3 | 789 | 24 | 3.0 | 0.0234 | 0.57 ( 0.35, 0.93) | 0.56 ( 0.34, 0.93) | -0.02 (-0.04, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.4259 |
| <75 | 500 | 39 | 7.8 | 500 | 17 | 3.4 | 0.0025 | 0.44 ( 0.25, 0.76) | 0.42 ( 0.23, 0.75) | -0.04 (-0.07,-0.02) | |
| 75 to <85 | 427 | 19 | 4.4 | 417 | 14 | 3.4 | 0.4130 | 0.75 ( 0.38, 1.48) | 0.75 ( 0.37, 1.51) | -0.01 (-0.04, 0.02) | |
| >=85 | 261 | 10 | 3.8 | 254 | 4 | 1.6 | 0.1154 | 0.41 ( 0.13, 1.29) | 0.40 ( 0.12, 1.30) | -0.02 (-0.05, 0.01) | |
| History of heart failure | | | | | | | | | | | 0.5355 |
| No | 1048 | 51 | 4.9 | 1031 | 28 | 2.7 | 0.0103 | 0.56 ( 0.35, 0.88) | 0.55 ( 0.34, 0.87) | -0.02 (-0.04,-0.01) | |
| Yes | 140 | 17 | 12.1 | 140 | 7 | 5.0 | 0.0328 | 0.41 ( 0.18, 0.96) | 0.38 ( 0.15, 0.95) | -0.07 (-0.14,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Dyspnoea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.8181 |
| <45 | 179 | 16 | 8.9 | 178 | 9 | 5.1 | 0.1507 | 0.57 ( 0.26, | 1.25) | 0.54 ( 0.23, | 1.26) | -0.04 (-0.09, 0.01) | |
| >=45 | 1009 | 52 | 5.2 | 993 | 26 | 2.6 | 0.0034 | 0.51 ( 0.32, | 0.81) | 0.49 ( 0.31, | 0.80) | -0.03 (-0.04,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.1217 |
| Normal (<30) | 250 | 14 | 5.6 | 257 | 6 | 2.3 | 0.0590 | 0.42 ( 0.16, | 1.07) | 0.40 ( 0.15, | 1.07) | -0.03 (-0.07, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 40 | 5.9 | 645 | 15 | 2.3 | 0.0011 | 0.39 ( 0.22, | 0.70) | 0.38 ( 0.21, | 0.69) | -0.04 (-0.06,-0.01) | |
| Macroalbuminuria (>300) | 260 | 14 | 5.4 | 261 | 14 | 5.4 | 0.9917 | 1.00 ( 0.48, | 2.05) | 1.00 ( 0.47, | 2.13) | 0.00 (-0.04, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.2510 |
| Low, moderate or high | 1018 | 55 | 5.4 | 1001 | 25 | 2.5 | 0.0008 | 0.46 ( 0.29, | 0.74) | 0.45 ( 0.28, | 0.73) | -0.03 (-0.05,-0.01) | |
| Very high | 167 | 13 | 7.8 | 162 | 10 | 6.2 | 0.5666 | 0.79 ( 0.36, | 1.76) | 0.78 ( 0.33, | 1.83) | -0.02 (-0.07, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.7262 |
| No | 205 | 13 | 6.3 | 211 | 8 | 3.8 | 0.2350 | 0.60 ( 0.25, | 1.41) | 0.58 ( 0.24, | 1.44) | -0.03 (-0.07, 0.02) | |
| Yes | 983 | 55 | 5.6 | 960 | 27 | 2.8 | 0.0023 | 0.50 ( 0.32, | 0.79) | 0.49 ( 0.31, | 0.78) | -0.03 (-0.05,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.8856 |
| No | 422 | 17 | 4.0 | 408 | 9 | 2.2 | 0.1318 | 0.55 ( 0.25, | 1.21) | 0.54 ( 0.24, | 1.22) | -0.02 (-0.04, 0.01) | |
| Yes | 766 | 51 | 6.7 | 763 | 26 | 3.4 | 0.0037 | 0.51 ( 0.32, | 0.81) | 0.49 ( 0.31, | 0.80) | -0.03 (-0.05,-0.01) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.1088 |
| No | 629 | 22 | 3.5 | 589 | 16 | 2.7 | 0.4333 | 0.78 ( 0.41, | 1.46) | 0.77 ( 0.40, | 1.48) | -0.01 (-0.03, 0.01) | |
| Yes | 559 | 46 | 8.2 | 582 | 19 | 3.3 | 0.0003 | 0.40 ( 0.24, | 0.67) | 0.38 ( 0.22, | 0.65) | -0.05 (-0.08,-0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Oropharyngeal pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 24 | 2.0 | 1171 | 13 | 1.1 | 0.0753 | 0.55 ( 0.28, 1.07) | 0.54 ( 0.28, 1.07) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Chronic obstructive pulmonary disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 21 | 1.8 | 1171 | 14 | 1.2 | 0.2505 | 0.68 ( 0.35, 1.32) | 0.67 ( 0.34, 1.33) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Sleep apnoea syndrome

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 18 | 1.5 | 1171 | 5 | 0.4 | 0.0072 | 0.28 | ( 0.10, 0.76) | 0.28 | ( 0.10, 0.75) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.3365 |
| Male | 864 | 13 | 1.5 | 837 | 5 | 0.6 | 0.0675 | 0.40 | ( 0.14, 1.11) | 0.39 | ( 0.14, 1.11) | -0.01 | (-0.02, 0.00) | |
| Female | 324 | 5 | 1.5 | 334 | 0 | 0 | 0.0368 | 0.09 | (<0.01, 1.59) | 0.09 | (<0.01, 1.58) | -0.02 | (-0.03, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.3110 |
| <65 | 569 | 12 | 2.1 | 547 | 2 | 0.4 | 0.0089 | 0.17 | ( 0.04, 0.77) | 0.17 | ( 0.04, 0.76) | -0.02 | (-0.03, 0.00) | |
| >=65 | 619 | 6 | 1.0 | 624 | 3 | 0.5 | 0.3097 | 0.50 | ( 0.12, 1.97) | 0.49 | ( 0.12, 1.98) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.8596 |
| Europe | 468 | 8 | 1.7 | 434 | 2 | 0.5 | 0.0736 | 0.27 | ( 0.06, 1.26) | 0.27 | ( 0.06, 1.26) | -0.01 | (-0.03, 0.00) | |
| North America | 259 | 9 | 3.5 | 241 | 2 | 0.8 | 0.0439 | 0.24 | ( 0.05, 1.09) | 0.23 | ( 0.05, 1.09) | -0.03 | (-0.05, 0.00) | |
| Latin America | 177 | 0 | 0 | 191 | 0 | 0 | 0.9698 | 0.93 | ( 0.02, 46.47) | 0.93 | ( 0.02, 46.96) | 0.00 | (-0.01, 0.01) | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | 0.9697 | 0.93 | ( 0.02, 45.87) | 0.93 | ( 0.02, 47.58) | 0.00 | (-0.04, 0.04) | |
| Asia | 234 | 1 | 0.4 | 251 | 1 | 0.4 | 0.9604 | 0.93 | ( 0.06, 14.82) | 0.93 | ( 0.06, 14.99) | 0.00 | (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3347 |
| <30 | 554 | 5 | 0.9 | 566 | 0 | 0 | 0.0382 | 0.09 | (<0.01, 1.61) | 0.09 | (<0.01, 1.60) | -0.01 | (-0.02, 0.00) | |
| >=30 | 634 | 13 | 2.1 | 605 | 5 | 0.8 | 0.0719 | 0.40 | ( 0.14, 1.12) | 0.40 | ( 0.14, 1.12) | -0.01 | (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8337 |
| <130 | 379 | 8 | 2.1 | 382 | 2 | 0.5 | 0.0545 | 0.25 | ( 0.05, 1.16) | 0.24 | ( 0.05, 1.16) | -0.02 | (-0.03, 0.00) | |
| >=130 | 809 | 10 | 1.2 | 789 | 3 | 0.4 | 0.0569 | 0.31 | ( 0.08, 1.11) | 0.30 | ( 0.08, 1.11) | -0.01 | (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3892 |
| <75 | 500 | 7 | 1.4 | 500 | 4 | 0.8 | 0.3631 | 0.57 | ( 0.17, 1.94) | 0.57 | ( 0.17, 1.95) | -0.01 | (-0.02, 0.01) | |
| 75 to <85 | 427 | 6 | 1.4 | 417 | 0 | 0 | 0.0247 | 0.08 | (<0.01, 1.39) | 0.08 | (<0.01, 1.38) | -0.01 | (-0.03, 0.00) | |
| >=85 | 261 | 5 | 1.9 | 254 | 1 | 0.4 | 0.1076 | 0.21 | ( 0.02, 1.75) | 0.20 | ( 0.02, 1.74) | -0.02 | (-0.03, 0.00) | |
| History of heart failure | | | | | | | | | | | | | | 0.2729 |
| No | 1048 | 12 | 1.1 | 1031 | 5 | 0.5 | 0.0947 | 0.42 | ( 0.15, 1.20) | 0.42 | ( 0.15, 1.20) | -0.01 | (-0.01, 0.00) | |
| Yes | 140 | 6 | 4.3 | 140 | 0 | 0 | 0.0216 | 0.08 | (<0.01, 1.35) | 0.07 | (<0.01, 1.32) | -0.04 | (-0.08,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Sleep apnoea syndrome

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.6064 |
| <45 | 179 | 5 | 2.8 | 178 | 2 | 1.1 | 0.2552 | 0.40 | ( 0.08, 2.05) | 0.40 | ( 0.08, 2.07) | -0.02 (-0.05, 0.01) | |
| >=45 | 1009 | 13 | 1.3 | 993 | 3 | 0.3 | 0.0132 | 0.23 | ( 0.07, 0.82) | 0.23 | ( 0.07, 0.82) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.5518 |
| Normal (<30) | 250 | 1 | 0.4 | 257 | 1 | 0.4 | 0.9844 | 0.97 | ( 0.06, 15.47) | 0.97 | ( 0.06, 15.64) | 0.00 (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 10 | 1.5 | 645 | 3 | 0.5 | 0.0616 | 0.31 | ( 0.09, 1.14) | 0.31 | ( 0.09, 1.13) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 260 | 7 | 2.7 | 261 | 1 | 0.4 | 0.0321 | 0.14 | ( 0.02, 1.15) | 0.14 | ( 0.02, 1.14) | -0.02 (-0.04, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.4475 |
| Low, moderate or high | 1018 | 11 | 1.1 | 1001 | 4 | 0.4 | 0.0748 | 0.37 | ( 0.12, 1.16) | 0.37 | ( 0.12, 1.16) | -0.01 (-0.01, 0.00) | |
| Very high | 167 | 7 | 4.2 | 162 | 1 | 0.6 | 0.0354 | 0.15 | ( 0.02, 1.18) | 0.14 | ( 0.02, 1.17) | -0.04 (-0.07, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.9660 |
| No | 205 | 1 | 0.5 | 211 | 0 | 0 | 0.4659 | 0.32 | ( 0.01, 7.91) | 0.32 | ( 0.01, 7.96) | 0.00 (-0.02, 0.01) | |
| Yes | 983 | 17 | 1.7 | 960 | 5 | 0.5 | 0.0118 | 0.30 | ( 0.11, 0.81) | 0.30 | ( 0.11, 0.81) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.7450 |
| No | 422 | 5 | 1.2 | 408 | 1 | 0.2 | 0.1101 | 0.21 | ( 0.02, 1.76) | 0.20 | ( 0.02, 1.76) | -0.01 (-0.02, 0.00) | |
| Yes | 766 | 13 | 1.7 | 763 | 4 | 0.5 | 0.0287 | 0.31 | ( 0.10, 0.94) | 0.31 | ( 0.10, 0.94) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.5323 |
| No | 629 | 5 | 0.8 | 589 | 2 | 0.3 | 0.2934 | 0.43 | ( 0.08, 2.19) | 0.43 | ( 0.08, 2.20) | 0.00 (-0.01, 0.00) | |
| Yes | 559 | 13 | 2.3 | 582 | 3 | 0.5 | 0.0093 | 0.22 | ( 0.06, 0.77) | 0.22 | ( 0.06, 0.77) | -0.02 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Asthma

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** | |
| Overall | 1188 | 15 | 1.3 | 1171 | 6 | 0.5 | 0.0524 | 0.41 ( 0.16, 1.04) | 0.40 ( 0.16, 1.04) | -0.01 (-0.02, 0.00) | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Dyspnoea exertional

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 8 | 0.7 | 0.2879 | 0.62 ( 0.26, 1.50) | 0.62 ( 0.26, 1.51) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Rhinitis allergic

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 6 | 0.5 | 0.1139 | 0.47 ( 0.18, 1.23) | 0.47 ( 0.18, 1.23) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 47 | 4.0 | 1171 | 40 | 3.4 | 0.4863 | 0.86 ( 0.57, | 1.31) | 0.86 ( 0.56, | 1.32) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Contusion

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 28 | 2.4 | 1171 | 18 | 1.5 | 0.1500 | 0.65 ( 0.36, 1.17) | 0.65 ( 0.36, 1.18) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Wound

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 23 | 1.9 | 1171 | 24 | 2.0 | 0.8436 | 1.06 ( 0.60, 1.86) | 1.06 ( 0.59, 1.89) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Ligament sprain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 20 | 1.7 | 1171 | 10 | 0.9 | 0.0722 | 0.51 ( 0.24, 1.08) | 0.50 ( 0.23, 1.08) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Limb injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 11 | 0.9 | 0.4521 | 0.74 ( 0.34, 1.61) | 0.74 ( 0.34, 1.62) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Laceration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 13 | 1.1 | 0.8124 | 1.10 ( 0.50, 2.40) | 1.10 ( 0.50, 2.42) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Skin abrasion

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 13 | 1.1 | 0.8124 | 1.10 ( 0.50, 2.40) | 1.10 ( 0.50, 2.42) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Skin ulcer

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 41 | 3.5 | 1171 | 30 | 2.6 | 0.2063 | 0.74 ( 0.47, 1.18) | 0.74 ( 0.46, 1.19) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Pruritus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 25 | 2.1 | 1171 | 19 | 1.6 | 0.3871 | 0.77 ( 0.43, 1.39) | 0.77 ( 0.42, 1.40) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Rash

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 19 | 1.6 | 1171 | 22 | 1.9 | 0.6036 | 1.17 ( 0.64, 2.16) | 1.18 ( 0.63, 2.19) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Eczema

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 22 | 1.9 | 1171 | 19 | 1.6 | 0.6700 | 0.88 ( 0.48, 1.61) | 0.87 ( 0.47, 1.62) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Diabetic foot

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 21 | 1.8 | 1171 | 13 | 1.1 | 0.1803 | 0.63 ( 0.32, 1.25) | 0.62 ( 0.31, 1.25) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Hyperhidrosis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 17 | 1.4 | 1171 | 8 | 0.7 | 0.0762 | 0.48 ( 0.21, 1.10) | 0.47 ( 0.20, 1.10) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Dry skin

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 5 | 0.4 | 1171 | 13 | 1.1 | 0.0544 | 2.64 ( 0.94, 7.38) | 2.66 ( 0.94, 7.47) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders
Preferred term: Cataract

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 70 | 5.9 | 1171 | 61 | 5.2 | 0.4689 | 0.88 ( 0.63, | 1.23) | 0.88 ( 0.62, | 1.25) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders
Preferred term: Diabetic retinopathy

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 30 | 2.5 | 1171 | 24 | 2.0 | 0.4398 | 0.81 ( 0.48, 1.38) | 0.81 ( 0.47, 1.39) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders
Preferred term: Glaucoma

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 5 | 0.4 | 1171 | 13 | 1.1 | 0.0544 | 2.64 ( 0.94, 7.38) | 2.66 ( 0.94, 7.47) | 0.01 ( 0.00, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 97 | 8.2 | 1171 | 60 | 5.1 | 0.0030 | 0.63 | ( 0.46, 0.86) | 0.61 | ( 0.44, 0.85) | -0.03 | (-0.05,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.6549 |
| Male | 864 | 66 | 7.6 | 837 | 42 | 5.0 | 0.0267 | 0.66 | ( 0.45, 0.96) | 0.64 | ( 0.43, 0.95) | -0.03 | (-0.05, 0.00) | |
| Female | 324 | 31 | 9.6 | 334 | 18 | 5.4 | 0.0412 | 0.56 | ( 0.32, 0.99) | 0.54 | ( 0.29, 0.98) | -0.04 | (-0.08, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.6571 |
| <65 | 569 | 43 | 7.6 | 547 | 28 | 5.1 | 0.0953 | 0.68 | ( 0.43, 1.07) | 0.66 | ( 0.40, 1.08) | -0.02 | (-0.05, 0.00) | |
| >=65 | 619 | 54 | 8.7 | 624 | 32 | 5.1 | 0.0125 | 0.59 | ( 0.39, 0.90) | 0.57 | ( 0.36, 0.89) | -0.04 | (-0.06,-0.01) | |
| Region | | | | | | | | | | | | | | 0.1692 |
| Europe | 468 | 25 | 5.3 | 434 | 23 | 5.3 | 0.9774 | 0.99 | ( 0.57, 1.72) | 0.99 | ( 0.55, 1.77) | 0.00 | (-0.03, 0.03) | |
| North America | 259 | 25 | 9.7 | 241 | 10 | 4.1 | 0.0160 | 0.43 | ( 0.21, 0.88) | 0.41 | ( 0.19, 0.86) | -0.06 | (-0.10,-0.01) | |
| Latin America | 177 | 22 | 12.4 | 191 | 11 | 5.8 | 0.0252 | 0.46 | ( 0.23, 0.93) | 0.43 | ( 0.20, 0.92) | -0.07 | (-0.13,-0.01) | |
| Africa | 50 | 6 | 12.0 | 54 | 1 | 1.9 | 0.0390 | 0.15 | ( 0.02, 1.24) | 0.14 | ( 0.02, 1.19) | -0.10 | (-0.20, 0.00) | |
| Asia | 234 | 19 | 8.1 | 251 | 15 | 6.0 | 0.3555 | 0.74 | ( 0.38, 1.41) | 0.72 | ( 0.36, 1.45) | -0.02 | (-0.07, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7622 |
| <30 | 554 | 51 | 9.2 | 566 | 34 | 6.0 | 0.0433 | 0.65 | ( 0.43, 0.99) | 0.63 | ( 0.40, 0.99) | -0.03 | (-0.06, 0.00) | |
| >=30 | 634 | 46 | 7.3 | 605 | 26 | 4.3 | 0.0261 | 0.59 | ( 0.37, 0.95) | 0.57 | ( 0.35, 0.94) | -0.03 | (-0.06, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3893 |
| <130 | 379 | 33 | 8.7 | 382 | 17 | 4.5 | 0.0178 | 0.51 | ( 0.29, 0.90) | 0.49 | ( 0.27, 0.89) | -0.04 | (-0.08,-0.01) | |
| >=130 | 809 | 64 | 7.9 | 789 | 43 | 5.4 | 0.0491 | 0.69 | ( 0.47, >1.00) | 0.67 | ( 0.45, 1.00) | -0.02 | (-0.05, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0074 |
| <75 | 500 | 45 | 9.0 | 500 | 27 | 5.4 | 0.0277 | 0.60 | ( 0.38, 0.95) | 0.58 | ( 0.35, 0.95) | -0.04 | (-0.07, 0.00) | |
| 75 to <85 | 427 | 38 | 8.9 | 417 | 13 | 3.1 | 0.0004 | 0.35 | ( 0.19, 0.65) | 0.33 | ( 0.17, 0.63) | -0.06 | (-0.09,-0.03) | |
| >=85 | 261 | 14 | 5.4 | 254 | 20 | 7.9 | 0.2514 | 1.47 | ( 0.76, 2.84) | 1.51 | ( 0.74, 3.05) | 0.03 | (-0.02, 0.07) | |
| History of heart failure | | | | | | | | | | | | | | 0.4686 |
| No | 1048 | 82 | 7.8 | 1031 | 48 | 4.7 | 0.0028 | 0.60 | ( 0.42, 0.84) | 0.58 | ( 0.40, 0.83) | -0.03 | (-0.05,-0.01) | |
| Yes | 140 | 15 | 10.7 | 140 | 12 | 8.6 | 0.5436 | 0.80 | ( 0.39, 1.65) | 0.78 | ( 0.35, 1.74) | -0.02 | (-0.09, 0.05) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.5915 |
| <45 | 179 | 26 | 14.5 | 178 | 14 | 7.9 | 0.0461 | 0.54 ( 0.29, >1.00) | 0.50 ( 0.25, 1.00) | -0.07 (-0.13, 0.00) | |
| >=45 | 1009 | 71 | 7.0 | 993 | 46 | 4.6 | 0.0219 | 0.66 ( 0.46, 0.94) | 0.64 ( 0.44, 0.94) | -0.02 (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.9897 |
| Normal (<30) | 250 | 18 | 7.2 | 257 | 11 | 4.3 | 0.1569 | 0.59 ( 0.29, 1.23) | 0.58 ( 0.27, 1.25) | -0.03 (-0.07, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 46 | 6.8 | 645 | 27 | 4.2 | 0.0367 | 0.61 ( 0.39, 0.98) | 0.60 ( 0.37, 0.97) | -0.03 (-0.05, 0.00) | |
| Macroalbuminuria (>300) | 260 | 33 | 12.7 | 261 | 21 | 8.0 | 0.0819 | 0.63 ( 0.38, 1.07) | 0.60 ( 0.34, 1.07) | -0.05 (-0.10, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.4839 |
| Low, moderate or high | 1018 | 69 | 6.8 | 1001 | 45 | 4.5 | 0.0263 | 0.66 ( 0.46, 0.96) | 0.65 ( 0.44, 0.95) | -0.02 (-0.04, 0.00) | |
| Very high | 167 | 28 | 16.8 | 162 | 14 | 8.6 | 0.0273 | 0.52 ( 0.28, 0.94) | 0.47 ( 0.24, 0.93) | -0.08 (-0.15,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3034 |
| No | 205 | 20 | 9.8 | 211 | 9 | 4.3 | 0.0279 | 0.44 ( 0.20, 0.94) | 0.41 ( 0.18, 0.93) | -0.05 (-0.10,-0.01) | |
| Yes | 983 | 77 | 7.8 | 960 | 51 | 5.3 | 0.0251 | 0.68 ( 0.48, 0.96) | 0.66 ( 0.46, 0.95) | -0.03 (-0.05, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.8520 |
| No | 422 | 36 | 8.5 | 408 | 21 | 5.1 | 0.0540 | 0.60 ( 0.36, 1.02) | 0.58 ( 0.33, 1.01) | -0.03 (-0.07, 0.00) | |
| Yes | 766 | 61 | 8.0 | 763 | 39 | 5.1 | 0.0241 | 0.64 ( 0.43, 0.95) | 0.62 ( 0.41, 0.94) | -0.03 (-0.05, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.4668 |
| No | 629 | 39 | 6.2 | 589 | 26 | 4.4 | 0.1658 | 0.71 ( 0.44, 1.15) | 0.70 ( 0.42, 1.16) | -0.02 (-0.04, 0.01) | |
| Yes | 559 | 58 | 10.4 | 582 | 34 | 5.8 | 0.0049 | 0.56 ( 0.37, 0.85) | 0.54 ( 0.35, 0.83) | -0.05 (-0.08,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Eosinophilia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 15 | 1.3 | 0.8213 | 1.09 ( 0.53, 2.24) | 1.09 ( 0.52, 2.26) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Thrombocytopenia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 9 | 0.8 | 0.2319 | 0.61 ( 0.27, 1.39) | 0.61 ( 0.26, 1.39) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Insomnia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 41 | 3.5 | 1171 | 29 | 2.5 | 0.1631 | 0.72 ( 0.45, 1.15) | 0.71 ( 0.44, 1.15) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Depression

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 39 | 3.3 | 1171 | 28 | 2.4 | 0.1924 | 0.73 ( 0.45, 1.18) | 0.72 ( 0.44, 1.18) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Anxiety

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 35 | 2.9 | 1171 | 29 | 2.5 | 0.4827 | 0.84 ( 0.52, 1.37) | 0.84 ( 0.51, 1.38) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Reproductive system and breast disorders
Preferred term: Benign prostatic hyperplasia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 33 | 2.8 | 1171 | 22 | 1.9 | 0.1480 | 0.68 ( 0.40, 1.15) | 0.67 ( 0.39, 1.16) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Reproductive system and breast disorders
Preferred term: Balanoposthitis

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 1188 | 2 | 0.2 | 1171 | 14 | 1.2 | 0.0024 | 7.10 ( 1.62, 31.18) | 7.18 ( 1.63, 31.64) | 0.01 ( 0.00, 0.02) | |
| Sex | | | | | | | | | | | 0.3472 |
| Male | 864 | 2 | 0.2 | 837 | 14 | 1.7 | 0.0021 | 7.23 ( 1.65, 31.70) | 7.33 ( 1.66, 32.36) | 0.01 ( 0.01, 0.02) | |
| Female | 324 | 0 | 0 | 334 | 0 | 0 | 0.9879 | 0.97 ( 0.02, 48.75) | 0.97 ( 0.02, 49.04) | 0.00 (-0.01, 0.01) | |
| Age [years] | | | | | | | | | | | |
| <65 | 569 | 0 | 0 | 547 | 9 | 1.6 | | | | | |
| >=65 | 619 | 2 | 0.3 | 624 | 5 | 0.8 | | | | | |
| Region | | | | | | | | | | | |
| Europe | 468 | 2 | 0.4 | 434 | 7 | 1.6 | | | | | |
| North America | 259 | 0 | 0 | 241 | 3 | 1.2 | | | | | |
| Latin America | 177 | 0 | 0 | 191 | 3 | 1.6 | | | | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | | | | | |
| Asia | 234 | 0 | 0 | 251 | 1 | 0.4 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | 0.6656 |
| <30 | 554 | 1 | 0.2 | 566 | 5 | 0.9 | 0.1071 | 4.89 ( 0.57, 41.76) | 4.93 ( 0.57, 42.32) | 0.01 ( 0.00, 0.02) | |
| >=30 | 634 | 1 | 0.2 | 605 | 9 | 1.5 | 0.0089 | 9.43 ( 1.20, 74.22) | 9.56 ( 1.21, 75.68) | 0.01 ( 0.00, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | 0.7408 |
| <130 | 379 | 0 | 0 | 382 | 4 | 1.0 | 0.0741 | 8.93 ( 0.48,165.28) | 9.02 ( 0.48,168.19) | 0.01 ( 0.00, 0.02) | |
| >=130 | 809 | 2 | 0.2 | 789 | 10 | 1.3 | 0.0182 | 5.13 ( 1.13, 23.32) | 5.18 ( 1.13, 23.72) | 0.01 ( 0.00, 0.02) | |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 500 | 2 | 0.4 | 500 | 4 | 0.8 | | | | | |
| 75 to <85 | 427 | 0 | 0 | 417 | 6 | 1.4 | | | | | |
| >=85 | 261 | 0 | 0 | 254 | 4 | 1.6 | | | | | |
| History of heart failure | | | | | | | | | | | 0.3579 |
| No | 1048 | 2 | 0.2 | 1031 | 14 | 1.4 | 0.0023 | 7.12 ( 1.62, 31.23) | 7.20 ( 1.63, 31.76) | 0.01 ( 0.00, 0.02) | |
| Yes | 140 | 0 | 0 | 140 | 0 | 0 | 1.0000 | 1.00 ( 0.02, 50.05) | 1.00 ( 0.02, 50.75) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Reproductive system and breast disorders
Preferred term: Balanoposthitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0521 |
| <45 | 179 | 1 | 0.6 | 178 | 0 | 0 | 0.4807 | 0.34 ( 0.01, 8.17) | 0.33 ( 0.01, 8.24) | -0.01 (-0.02, 0.01) | |
| >=45 | 1009 | 1 | 0.1 | 993 | 14 | 1.4 | 0.0007 | 14.23 ( 1.87,107.98) | 14.41 ( 1.89,109.83) | 0.01 ( 0.01, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 250 | 1 | 0.4 | 257 | 4 | 1.6 | | | | | |
| Microalbuminuria (30 to <=300) | 675 | 1 | 0.1 | 645 | 5 | 0.8 | | | | | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 5 | 1.9 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.0536 |
| Low, moderate or high | 1018 | 1 | 0.1 | 1001 | 14 | 1.4 | 0.0007 | 14.24 ( 1.88,108.07) | 14.43 ( 1.89,109.91) | 0.01 ( 0.01, 0.02) | |
| Very high | 167 | 1 | 0.6 | 162 | 0 | 0 | 0.4915 | 0.34 ( 0.01, 8.37) | 0.34 ( 0.01, 8.45) | -0.01 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3494 |
| No | 205 | 0 | 0 | 211 | 0 | 0 | 0.9885 | 0.97 ( 0.02, 48.74) | 0.97 ( 0.02, 49.20) | 0.00 (-0.01, 0.01) | |
| Yes | 983 | 2 | 0.2 | 960 | 14 | 1.5 | 0.0022 | 7.17 ( 1.63, 31.45) | 7.26 ( 1.65, 32.03) | 0.01 ( 0.00, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.7132 |
| No | 422 | 1 | 0.2 | 408 | 5 | 1.2 | 0.0928 | 5.17 ( 0.61, 44.07) | 5.22 ( 0.61, 44.90) | 0.01 ( 0.00, 0.02) | |
| Yes | 766 | 1 | 0.1 | 763 | 9 | 1.2 | 0.0109 | 9.04 ( 1.15, 71.14) | 9.13 ( 1.15, 72.25) | 0.01 ( 0.00, 0.02) | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 0 | 0 | 589 | 9 | 1.5 | | | | | |
| Yes | 559 | 2 | 0.4 | 582 | 5 | 0.9 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Ear and labyrinth disorders
Preferred term: Vertigo

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 41 | 3.5 | 1171 | 22 | 1.9 | 0.0179 | 0.54 | ( 0.33, 0.91) | 0.54 | ( 0.32, 0.90) | -0.02 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.9795 |
| Male | 864 | 21 | 2.4 | 837 | 11 | 1.3 | 0.0902 | 0.54 | ( 0.26, 1.11) | 0.53 | ( 0.26, 1.12) | -0.01 | (-0.02, 0.00) | |
| Female | 324 | 20 | 6.2 | 334 | 11 | 3.3 | 0.0814 | 0.53 | ( 0.26, 1.10) | 0.52 | ( 0.24, 1.10) | -0.03 | (-0.06, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.9174 |
| <65 | 569 | 14 | 2.5 | 547 | 7 | 1.3 | 0.1467 | 0.52 | ( 0.21, 1.28) | 0.51 | ( 0.21, 1.28) | -0.01 | (-0.03, 0.00) | |
| >=65 | 619 | 27 | 4.4 | 624 | 15 | 2.4 | 0.0561 | 0.55 | ( 0.30, 1.03) | 0.54 | ( 0.28, 1.03) | -0.02 | (-0.04, 0.00) | |
| Region | | | | | | | | | | | | | | 0.4966 |
| Europe | 468 | 16 | 3.4 | 434 | 5 | 1.2 | 0.0241 | 0.34 | ( 0.12, 0.91) | 0.33 | ( 0.12, 0.91) | -0.02 | (-0.04, 0.00) | |
| North America | 259 | 13 | 5.0 | 241 | 6 | 2.5 | 0.1393 | 0.50 | ( 0.19, 1.28) | 0.48 | ( 0.18, 1.29) | -0.03 | (-0.06, 0.01) | |
| Latin America | 177 | 4 | 2.3 | 191 | 2 | 1.0 | 0.3587 | 0.46 | ( 0.09, 2.50) | 0.46 | ( 0.08, 2.53) | -0.01 | (-0.04, 0.01) | |
| Africa | 50 | 2 | 4.0 | 54 | 1 | 1.9 | 0.5131 | 0.46 | ( 0.04, 4.95) | 0.45 | ( 0.04, 5.15) | -0.02 | (-0.09, 0.04) | |
| Asia | 234 | 6 | 2.6 | 251 | 8 | 3.2 | 0.6821 | 1.24 | ( 0.44, 3.53) | 1.25 | ( 0.43, 3.66) | 0.01 | (-0.02, 0.04) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3833 |
| <30 | 554 | 17 | 3.1 | 566 | 12 | 2.1 | 0.3177 | 0.69 | ( 0.33, 1.43) | 0.68 | ( 0.32, 1.45) | -0.01 | (-0.03, 0.01) | |
| >=30 | 634 | 24 | 3.8 | 605 | 10 | 1.7 | 0.0216 | 0.44 | ( 0.21, 0.91) | 0.43 | ( 0.20, 0.90) | -0.02 | (-0.04, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1673 |
| <130 | 379 | 14 | 3.7 | 382 | 4 | 1.0 | 0.0163 | 0.28 | ( 0.09, 0.85) | 0.28 | ( 0.09, 0.85) | -0.03 | (-0.05, 0.00) | |
| >=130 | 809 | 27 | 3.3 | 789 | 18 | 2.3 | 0.2020 | 0.68 | ( 0.38, 1.23) | 0.68 | ( 0.37, 1.24) | -0.01 | (-0.03, 0.01) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1191 |
| <75 | 500 | 20 | 4.0 | 500 | 14 | 2.8 | 0.2951 | 0.70 | ( 0.36, 1.37) | 0.69 | ( 0.35, 1.38) | -0.01 | (-0.03, 0.01) | |
| 75 to <85 | 427 | 16 | 3.7 | 417 | 3 | 0.7 | 0.0030 | 0.19 | ( 0.06, 0.65) | 0.19 | ( 0.05, 0.64) | -0.03 | (-0.05,-0.01) | |
| >=85 | 261 | 5 | 1.9 | 254 | 5 | 2.0 | 0.9654 | 1.03 | ( 0.30, 3.51) | 1.03 | ( 0.29, 3.59) | 0.00 | (-0.02, 0.02) | |
| History of heart failure | | | | | | | | | | | | | | 0.3795 |
| No | 1048 | 34 | 3.2 | 1031 | 20 | 1.9 | 0.0615 | 0.60 | ( 0.35, 1.03) | 0.59 | ( 0.34, 1.03) | -0.01 | (-0.03, 0.00) | |
| Yes | 140 | 7 | 5.0 | 140 | 2 | 1.4 | 0.0902 | 0.29 | ( 0.06, 1.35) | 0.28 | ( 0.06, 1.35) | -0.04 | (-0.08, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Ear and labyrinth disorders
Preferred term: Vertigo

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.2815 |
| <45 | 179 | 8 | 4.5 | 178 | 2 | 1.1 | 0.0554 | 0.25 ( 0.05, | 1.17) | 0.24 ( 0.05, | 1.16) | -0.03 (-0.07, 0.00) | |
| >=45 | 1009 | 33 | 3.3 | 993 | 20 | 2.0 | 0.0800 | 0.62 ( 0.36, | 1.07) | 0.61 ( 0.35, | 1.07) | -0.01 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.0227 |
| Normal (<30) | 250 | 16 | 6.4 | 257 | 5 | 1.9 | 0.0119 | 0.30 ( 0.11, | 0.82) | 0.29 ( 0.10, | 0.80) | -0.04 (-0.08,-0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 21 | 3.1 | 645 | 8 | 1.2 | 0.0205 | 0.40 ( 0.18, | 0.89) | 0.39 ( 0.17, | 0.89) | -0.02 (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 260 | 4 | 1.5 | 261 | 9 | 3.4 | 0.1623 | 2.24 ( 0.70, | 7.19) | 2.29 ( 0.69, | 7.52) | 0.02 (-0.01, 0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.1602 |
| Low, moderate or high | 1018 | 37 | 3.6 | 1001 | 17 | 1.7 | 0.0070 | 0.47 ( 0.26, | 0.82) | 0.46 ( 0.26, | 0.82) | -0.02 (-0.03,-0.01) | |
| Very high | 167 | 4 | 2.4 | 162 | 5 | 3.1 | 0.7008 | 1.29 ( 0.35, | 4.71) | 1.30 ( 0.34, | 4.92) | 0.01 (-0.03, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.6386 |
| No | 205 | 7 | 3.4 | 211 | 5 | 2.4 | 0.5244 | 0.69 ( 0.22, | 2.15) | 0.69 ( 0.21, | 2.20) | -0.01 (-0.04, 0.02) | |
| Yes | 983 | 34 | 3.5 | 960 | 17 | 1.8 | 0.0200 | 0.51 ( 0.29, | 0.91) | 0.50 ( 0.28, | 0.91) | -0.02 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.4901 |
| No | 422 | 10 | 2.4 | 408 | 7 | 1.7 | 0.5061 | 0.72 ( 0.28, | 1.88) | 0.72 ( 0.27, | 1.91) | -0.01 (-0.03, 0.01) | |
| Yes | 766 | 31 | 4.0 | 763 | 15 | 2.0 | 0.0172 | 0.49 ( 0.26, | 0.89) | 0.48 ( 0.25, | 0.89) | -0.02 (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | 0.1520 |
| No | 629 | 14 | 2.2 | 589 | 11 | 1.9 | 0.6595 | 0.84 ( 0.38, | 1.83) | 0.84 ( 0.38, | 1.86) | 0.00 (-0.02, 0.01) | |
| Yes | 559 | 27 | 4.8 | 582 | 11 | 1.9 | 0.0057 | 0.39 ( 0.20, | 0.78) | 0.38 ( 0.19, | 0.77) | -0.03 (-0.05,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders
Preferred term: Cholelithiasis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 25 | 2.1 | 1171 | 19 | 1.6 | 0.3871 | 0.77 ( 0.43, 1.39) | 0.77 ( 0.42, 1.40) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders
Preferred term: Hepatic steatosis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 9 | 0.8 | 0.3111 | 0.65 ( 0.28, 1.50) | 0.65 ( 0.28, 1.51) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Endocrine disorders
Preferred term: Hypothyroidism

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 8 | 0.7 | 0.2879 | 0.62 ( 0.26, 1.50) | 0.62 ( 0.26, 1.51) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina unstable

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 53 | 4.5 | 1171 | 41 | 3.5 | 0.2333 | 0.78 ( 0.53, 1.17) | 0.78 ( 0.51, 1.18) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 49 | 4.1 | 1171 | 34 | 2.9 | 0.1075 | 0.70 ( 0.46, 1.08) | 0.70 ( 0.45, 1.08) | -0.01 (-0.03, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 1188 | 43 | 3.6 | 1171 | 23 | 2.0 | 0.0148 | 0.54 | ( 0.33, 0.89) | 0.53 | ( 0.32, 0.89) | -0.02 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0561 |
| Male | 864 | 26 | 3.0 | 837 | 19 | 2.3 | 0.3422 | 0.75 | ( 0.42, 1.35) | 0.75 | ( 0.41, 1.36) | -0.01 | (-0.02, 0.01) | |
| Female | 324 | 17 | 5.2 | 334 | 4 | 1.2 | 0.0031 | 0.23 | ( 0.08, 0.67) | 0.22 | ( 0.07, 0.66) | -0.04 | (-0.07,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.0347 |
| <65 | 569 | 15 | 2.6 | 547 | 14 | 2.6 | 0.9358 | 0.97 | ( 0.47, 1.99) | 0.97 | ( 0.46, 2.03) | 0.00 | (-0.02, 0.02) | |
| >=65 | 619 | 28 | 4.5 | 624 | 9 | 1.4 | 0.0014 | 0.32 | ( 0.15, 0.67) | 0.31 | ( 0.14, 0.66) | -0.03 | (-0.05,-0.01) | |
| Region | | | | | | | | | | | | | | 0.4493 |
| Europe | 468 | 8 | 1.7 | 434 | 6 | 1.4 | 0.6915 | 0.81 | ( 0.28, 2.31) | 0.81 | ( 0.28, 2.34) | 0.00 | (-0.02, 0.01) | |
| North America | 259 | 20 | 7.7 | 241 | 6 | 2.5 | 0.0085 | 0.32 | ( 0.13, 0.79) | 0.31 | ( 0.12, 0.77) | -0.05 | (-0.09,-0.01) | |
| Latin America | 177 | 5 | 2.8 | 191 | 2 | 1.0 | 0.2123 | 0.37 | ( 0.07, 1.89) | 0.36 | ( 0.07, 1.90) | -0.02 | (-0.05, 0.01) | |
| Africa | 50 | 4 | 8.0 | 54 | 2 | 3.7 | 0.3478 | 0.46 | ( 0.09, 2.42) | 0.44 | ( 0.08, 2.53) | -0.04 | (-0.13, 0.05) | |
| Asia | 234 | 6 | 2.6 | 251 | 7 | 2.8 | 0.8783 | 1.09 | ( 0.37, 3.19) | 1.09 | ( 0.36, 3.29) | 0.00 | (-0.03, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4867 |
| <30 | 554 | 18 | 3.2 | 566 | 8 | 1.4 | 0.0414 | 0.44 | ( 0.19, 0.99) | 0.43 | ( 0.18, 0.99) | -0.02 | (-0.04, 0.00) | |
| >=30 | 634 | 25 | 3.9 | 605 | 15 | 2.5 | 0.1451 | 0.63 | ( 0.33, 1.18) | 0.62 | ( 0.32, 1.19) | -0.01 | (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5178 |
| <130 | 379 | 20 | 5.3 | 382 | 9 | 2.4 | 0.0353 | 0.45 | ( 0.21, 0.97) | 0.43 | ( 0.19, 0.96) | -0.03 | (-0.06, 0.00) | |
| >=130 | 809 | 23 | 2.8 | 789 | 14 | 1.8 | 0.1556 | 0.62 | ( 0.32, 1.20) | 0.62 | ( 0.32, 1.21) | -0.01 | (-0.03, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9852 |
| <75 | 500 | 23 | 4.6 | 500 | 12 | 2.4 | 0.0584 | 0.52 | ( 0.26, 1.04) | 0.51 | ( 0.25, 1.04) | -0.02 | (-0.04, 0.00) | |
| 75 to <85 | 427 | 13 | 3.0 | 417 | 7 | 1.7 | 0.1921 | 0.55 | ( 0.22, 1.37) | 0.54 | ( 0.21, 1.38) | -0.01 | (-0.03, 0.01) | |
| >=85 | 261 | 7 | 2.7 | 254 | 4 | 1.6 | 0.3849 | 0.59 | ( 0.17, 1.98) | 0.58 | ( 0.17, 2.01) | -0.01 | (-0.04, 0.01) | |
| History of heart failure | | | | | | | | | | | | | | 0.2239 |
| No | 1048 | 29 | 2.8 | 1031 | 12 | 1.2 | 0.0086 | 0.42 | ( 0.22, 0.82) | 0.41 | ( 0.21, 0.82) | -0.02 | (-0.03, 0.00) | |
| Yes | 140 | 14 | 10.0 | 140 | 11 | 7.9 | 0.5295 | 0.79 | ( 0.37, 1.67) | 0.77 | ( 0.34, 1.75) | -0.02 | (-0.09, 0.05) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.0412 |
| <45 | 179 | 14 | 7.8 | 178 | 2 | 1.1 | 0.0022 | 0.14 ( 0.03, 0.62) | 0.13 ( 0.03, 0.60) | -0.07 (-0.11,-0.02) | |
| >=45 | 1009 | 29 | 2.9 | 993 | 21 | 2.1 | 0.2763 | 0.74 ( 0.42, 1.28) | 0.73 ( 0.41, 1.29) | -0.01 (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.7896 |
| Normal (<30) | 250 | 8 | 3.2 | 257 | 4 | 1.6 | 0.2236 | 0.49 ( 0.15, 1.59) | 0.48 ( 0.14, 1.61) | -0.02 (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 22 | 3.3 | 645 | 10 | 1.6 | 0.0436 | 0.48 ( 0.23, <1.00) | 0.47 ( 0.22, 0.99) | -0.02 (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 260 | 13 | 5.0 | 261 | 9 | 3.4 | 0.3785 | 0.69 ( 0.30, 1.59) | 0.68 ( 0.28, 1.62) | -0.02 (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.2726 |
| Low, moderate or high | 1018 | 28 | 2.8 | 1001 | 18 | 1.8 | 0.1516 | 0.65 ( 0.36, 1.17) | 0.65 ( 0.36, 1.18) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 15 | 9.0 | 162 | 5 | 3.1 | 0.0253 | 0.34 ( 0.13, 0.92) | 0.32 ( 0.11, 0.91) | -0.06 (-0.11,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.3859 |
| No | 205 | 9 | 4.4 | 211 | 3 | 1.4 | 0.0705 | 0.32 ( 0.09, 1.18) | 0.31 ( 0.08, 1.18) | -0.03 (-0.06, 0.00) | |
| Yes | 983 | 34 | 3.5 | 960 | 20 | 2.1 | 0.0652 | 0.60 ( 0.35, 1.04) | 0.59 ( 0.34, 1.04) | -0.01 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6082 |
| No | 422 | 10 | 2.4 | 408 | 4 | 1.0 | 0.1202 | 0.41 ( 0.13, 1.31) | 0.41 ( 0.13, 1.31) | -0.01 (-0.03, 0.00) | |
| Yes | 766 | 33 | 4.3 | 763 | 19 | 2.5 | 0.0499 | 0.58 ( 0.33, 1.01) | 0.57 ( 0.32, 1.01) | -0.02 (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.6925 |
| No | 629 | 10 | 1.6 | 589 | 4 | 0.7 | 0.1362 | 0.43 ( 0.13, 1.35) | 0.42 ( 0.13, 1.36) | -0.01 (-0.02, 0.00) | |
| Yes | 559 | 33 | 5.9 | 582 | 19 | 3.3 | 0.0326 | 0.55 ( 0.32, 0.96) | 0.54 ( 0.30, 0.96) | -0.03 (-0.05, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 37 | 3.1 | 1171 | 34 | 2.9 | 0.7643 | 0.93 ( 0.59, 1.47) | 0.93 ( 0.58, 1.49) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 31 | 2.6 | 1171 | 22 | 1.9 | 0.2312 | 0.72 ( 0.42, 1.24) | 0.71 ( 0.41, 1.24) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Coronary artery disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 31 | 2.6 | 1171 | 15 | 1.3 | 0.0196 | 0.49 ( 0.27, 0.90) | | 0.48 ( 0.26, 0.90) | | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | 0.3412 |
| Male | 864 | 25 | 2.9 | 837 | 10 | 1.2 | 0.0136 | 0.41 ( 0.20, 0.85) | | 0.41 ( 0.19, 0.85) | | -0.02 (-0.03, 0.00) | |
| Female | 324 | 6 | 1.9 | 334 | 5 | 1.5 | 0.7226 | 0.81 ( 0.25, 2.62) | | 0.81 ( 0.24, 2.67) | | 0.00 (-0.02, 0.02) | |
| Age [years] | | | | | | | | | | | | | 0.8628 |
| <65 | 569 | 14 | 2.5 | 547 | 7 | 1.3 | 0.1467 | 0.52 ( 0.21, 1.28) | | 0.51 ( 0.21, 1.28) | | -0.01 (-0.03, 0.00) | |
| >=65 | 619 | 17 | 2.7 | 624 | 8 | 1.3 | 0.0660 | 0.47 ( 0.20, 1.07) | | 0.46 ( 0.20, 1.07) | | -0.01 (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | 0.7004 |
| Europe | 468 | 10 | 2.1 | 434 | 6 | 1.4 | 0.3912 | 0.65 ( 0.24, 1.77) | | 0.64 ( 0.23, 1.78) | | -0.01 (-0.02, 0.01) | |
| North America | 259 | 12 | 4.6 | 241 | 3 | 1.2 | 0.0265 | 0.27 ( 0.08, 0.94) | | 0.26 ( 0.07, 0.93) | | -0.03 (-0.06, 0.00) | |
| Latin America | 177 | 5 | 2.8 | 191 | 2 | 1.0 | 0.2123 | 0.37 ( 0.07, 1.89) | | 0.36 ( 0.07, 1.90) | | -0.02 (-0.05, 0.01) | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | 0.9697 | 0.93 ( 0.02, 45.87) | | 0.93 ( 0.02, 47.58) | | 0.00 (-0.04, 0.04) | |
| Asia | 234 | 4 | 1.7 | 251 | 4 | 1.6 | 0.9203 | 0.93 ( 0.24, 3.69) | | 0.93 ( 0.23, 3.77) | | 0.00 (-0.02, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.6450 |
| <30 | 554 | 12 | 2.2 | 566 | 5 | 0.9 | 0.0792 | 0.41 ( 0.14, 1.15) | | 0.40 ( 0.14, 1.15) | | -0.01 (-0.03, 0.00) | |
| >=30 | 634 | 19 | 3.0 | 605 | 10 | 1.7 | 0.1178 | 0.55 ( 0.26, 1.18) | | 0.54 ( 0.25, 1.18) | | -0.01 (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.3639 |
| <130 | 379 | 10 | 2.6 | 382 | 3 | 0.8 | 0.0485 | 0.30 ( 0.08, 1.07) | | 0.29 ( 0.08, 1.07) | | -0.02 (-0.04, 0.00) | |
| >=130 | 809 | 21 | 2.6 | 789 | 12 | 1.5 | 0.1309 | 0.59 ( 0.29, 1.18) | | 0.58 ( 0.28, 1.19) | | -0.01 (-0.02, 0.00) | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.0519 |
| <75 | 500 | 16 | 3.2 | 500 | 5 | 1.0 | 0.0153 | 0.31 ( 0.12, 0.85) | | 0.31 ( 0.11, 0.84) | | -0.02 (-0.04, 0.00) | |
| 75 to <85 | 427 | 11 | 2.6 | 417 | 3 | 0.7 | 0.0347 | 0.28 ( 0.08, 0.99) | | 0.27 ( 0.08, 0.99) | | -0.02 (-0.04, 0.00) | |
| >=85 | 261 | 4 | 1.5 | 254 | 7 | 2.8 | 0.3371 | 1.80 ( 0.53, 6.07) | | 1.82 ( 0.53, 6.30) | | 0.01 (-0.01, 0.04) | |
| History of heart failure | | | | | | | | | | | | | 0.1670 |
| No | 1048 | 25 | 2.4 | 1031 | 15 | 1.5 | 0.1225 | 0.61 ( 0.32, 1.15) | | 0.60 ( 0.32, 1.15) | | -0.01 (-0.02, 0.00) | |
| Yes | 140 | 6 | 4.3 | 140 | 0 | 0 | 0.0216 | 0.08 (<0.01, 1.35) | | 0.07 (<0.01, 1.32) | | -0.04 (-0.08,-0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Coronary artery disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.5235 |
| <45 | 179 | 4 | 2.2 | 178 | 1 | 0.6 | 0.1787 | 0.25 ( 0.03, 2.23) | 0.25 ( 0.03, 2.23) | -0.02 (-0.04, 0.01) | |
| >=45 | 1009 | 27 | 2.7 | 993 | 14 | 1.4 | 0.0455 | 0.53 ( 0.28, <1.00) | 0.52 ( 0.27, 1.00) | -0.01 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.6153 |
| Normal (<30) | 250 | 7 | 2.8 | 257 | 4 | 1.6 | 0.3366 | 0.56 ( 0.16, 1.88) | 0.55 ( 0.16, 1.90) | -0.01 (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 675 | 16 | 2.4 | 645 | 9 | 1.4 | 0.1939 | 0.59 ( 0.26, 1.32) | 0.58 ( 0.26, 1.33) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 260 | 8 | 3.1 | 261 | 2 | 0.8 | 0.0546 | 0.25 ( 0.05, 1.16) | 0.24 ( 0.05, 1.16) | -0.02 (-0.05, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.9692 |
| Low, moderate or high | 1018 | 29 | 2.8 | 1001 | 14 | 1.4 | 0.0240 | 0.49 ( 0.26, 0.92) | 0.48 ( 0.25, 0.92) | -0.01 (-0.03, 0.00) | |
| Very high | 167 | 2 | 1.2 | 162 | 1 | 0.6 | 0.5798 | 0.52 ( 0.05, 5.63) | 0.51 ( 0.05, 5.71) | -0.01 (-0.03, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.0659 |
| No | 205 | 0 | 0 | 211 | 3 | 1.4 | 0.1393 | 6.80 ( 0.35,130.87) | 6.90 ( 0.35,134.41) | 0.01 ( 0.00, 0.03) | |
| Yes | 983 | 31 | 3.2 | 960 | 12 | 1.3 | 0.0043 | 0.40 ( 0.20, 0.77) | 0.39 ( 0.20, 0.76) | -0.02 (-0.03,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6860 |
| No | 422 | 3 | 0.7 | 408 | 2 | 0.5 | 0.6812 | 0.69 ( 0.12, 4.11) | 0.69 ( 0.11, 4.14) | 0.00 (-0.01, 0.01) | |
| Yes | 766 | 28 | 3.7 | 763 | 13 | 1.7 | 0.0182 | 0.47 ( 0.24, 0.89) | 0.46 ( 0.23, 0.89) | -0.02 (-0.04, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | 0.3957 |
| No | 629 | 13 | 2.1 | 589 | 4 | 0.7 | 0.0391 | 0.33 ( 0.11, >1.00) | 0.32 ( 0.11, 1.00) | -0.01 (-0.03, 0.00) | |
| Yes | 559 | 18 | 3.2 | 582 | 11 | 1.9 | 0.1536 | 0.59 ( 0.28, 1.23) | 0.58 ( 0.27, 1.24) | -0.01 (-0.03, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina pectoris

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 16 | 1.3 | 1171 | 22 | 1.9 | 0.3049 | 1.39 ( 0.74, 2.64) | 1.40 ( 0.73, 2.68) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 9 | 0.8 | 1171 | 17 | 1.5 | 0.1064 | 1.92 ( 0.86, 4.28) | 1.93 ( 0.86, 4.35) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 46 | 3.9 | 1171 | 38 | 3.2 | 0.4113 | 0.84 ( 0.55, 1.28) | 0.83 ( 0.54, 1.29) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Gastroenteritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 16 | 1.4 | 0.4244 | 1.35 ( 0.64, 2.85) | 1.36 ( 0.64, 2.88) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 13 | 1.1 | 0.8124 | 1.10 ( 0.50, 2.40) | 1.10 ( 0.50, 2.42) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Infections and infestations
Preferred term: Cellulitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 9 | 0.8 | 0.5323 | 0.76 ( 0.32, 1.80) | 0.76 ( 0.32, 1.81) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Cerebrovascular accident

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 23 | 1.9 | 1171 | 33 | 2.8 | 0.1594 | 1.46 ( 0.86, 2.46) | 1.47 ( 0.86, 2.52) | 0.01 ( 0.00, 0.02) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Transient ischaemic attack

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 17 | 1.4 | 1171 | 16 | 1.4 | 0.8937 | 0.95 ( 0.48, 1.88) | 0.95 ( 0.48, 1.90) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 13 | 1.1 | 0.8761 | 0.94 ( 0.44, 2.00) | 0.94 ( 0.44, 2.01) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

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System organ class: Vascular disorders
Preferred term: Peripheral arterial occlusive disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 17 | 1.4 | 1171 | 18 | 1.5 | 0.8311 | 1.07 ( 0.56, 2.07) | 1.08 ( 0.55, 2.10) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Chest pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 17 | 1.4 | 1171 | 21 | 1.8 | 0.4846 | 1.25 ( 0.66, 2.36) | 1.26 ( 0.66, 2.40) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 20 | 1.7 | 1171 | 12 | 1.0 | 0.1667 | 0.61 ( 0.30, 1.24) | 0.60 ( 0.29, 1.24) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 32 | 2.7 | 1171 | 22 | 1.9 | 0.1858 | 0.70 ( 0.41, 1.19) | 0.69 ( 0.40, 1.20) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 4 | 0.3 | 0.0479 | 0.34 ( 0.11, 1.05) | 0.34 ( 0.11, 1.04) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypoglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 6 | 0.5 | 0.0777 | 0.43 ( 0.17, 1.13) | 0.43 ( 0.17, 1.13) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 3 | 0.3 | 0.0132 | 0.23 ( 0.07, 0.82) | 0.23 ( 0.07, 0.82) | -0.01 (-0.01, 0.00) | | |
| Sex | | | | | | | | | | | | 0.3619 |
| Male | 864 | 8 | 0.9 | 837 | 3 | 0.4 | 0.1443 | 0.39 ( 0.10, 1.45) | 0.38 ( 0.10, 1.46) | -0.01 (-0.01, 0.00) | | |
| Female | 324 | 5 | 1.5 | 334 | 0 | 0 | 0.0368 | 0.09 (<0.01, 1.59) | 0.09 (<0.01, 1.58) | -0.02 (-0.03, 0.00) | | |
| Age [years] | | | | | | | | | | | | 0.8963 |
| <65 | 569 | 5 | 0.9 | 547 | 1 | 0.2 | 0.1120 | 0.21 ( 0.02, 1.78) | 0.21 ( 0.02, 1.77) | -0.01 (-0.02, 0.00) | | |
| >=65 | 619 | 8 | 1.3 | 624 | 2 | 0.3 | 0.0551 | 0.25 ( 0.05, 1.16) | 0.25 ( 0.05, 1.16) | -0.01 (-0.02, 0.00) | | |
| Region | | | | | | | | | | | | 0.7417 |
| Europe | 468 | 9 | 1.9 | 434 | 1 | 0.2 | 0.0153 | 0.12 ( 0.02, 0.94) | 0.12 ( 0.01, 0.93) | -0.02 (-0.03, 0.00) | | |
| North America | 259 | 1 | 0.4 | 241 | 1 | 0.4 | 0.9593 | 1.07 ( 0.07, 17.09) | 1.08 ( 0.07, 17.28) | 0.00 (-0.01, 0.01) | | |
| Latin America | 177 | 2 | 1.1 | 191 | 1 | 0.5 | 0.5181 | 0.46 ( 0.04, 5.07) | 0.46 ( 0.04, 5.12) | -0.01 (-0.02, 0.01) | | |
| Africa | 50 | 0 | 0 | 54 | 0 | 0 | 0.9697 | 0.93 ( 0.02, 45.87) | 0.93 ( 0.02, 47.58) | 0.00 (-0.04, 0.04) | | |
| Asia | 234 | 1 | 0.4 | 251 | 0 | 0 | 0.4482 | 0.31 ( 0.01, 7.59) | 0.31 ( 0.01, 7.63) | 0.00 (-0.02, 0.01) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7498 |
| <30 | 554 | 3 | 0.5 | 566 | 1 | 0.2 | 0.3062 | 0.33 ( 0.03, 3.13) | 0.33 ( 0.03, 3.13) | 0.00 (-0.01, 0.00) | | |
| >=30 | 634 | 10 | 1.6 | 605 | 2 | 0.3 | 0.0251 | 0.21 ( 0.05, 0.95) | 0.21 ( 0.05, 0.95) | -0.01 (-0.02, 0.00) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.4877 |
| <130 | 379 | 4 | 1.1 | 382 | 0 | 0 | 0.0713 | 0.11 (<0.01, 2.04) | 0.11 (<0.01, 2.03) | -0.01 (-0.02, 0.00) | | |
| >=130 | 809 | 9 | 1.1 | 789 | 3 | 0.4 | 0.0900 | 0.34 ( 0.09, 1.26) | 0.34 ( 0.09, 1.26) | -0.01 (-0.02, 0.00) | | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 500 | 6 | 1.2 | 500 | 0 | 0 | | | | | | |
| 75 to <85 | 427 | 4 | 0.9 | 417 | 2 | 0.5 | | | | | | |
| >=85 | 261 | 3 | 1.1 | 254 | 1 | 0.4 | | | | | | |
| History of heart failure | | | | | | | | | | | | 0.8455 |
| No | 1048 | 11 | 1.0 | 1031 | 3 | 0.3 | 0.0345 | 0.28 ( 0.08, 0.99) | 0.28 ( 0.08, 0.99) | -0.01 (-0.01, 0.00) | | |
| Yes | 140 | 2 | 1.4 | 140 | 0 | 0 | 0.2457 | 0.20 (<0.01, 4.13) | 0.20 (<0.01, 4.14) | -0.01 (-0.04, 0.01) | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.8743 |
| <45 | 179 | 1 | 0.6 | 178 | 0 | 0 | 0.4807 | 0.34 ( 0.01, 8.17) | 0.33 ( 0.01, 8.24) | -0.01 (-0.02, 0.01) | |
| >=45 | 1009 | 12 | 1.2 | 993 | 3 | 0.3 | 0.0214 | 0.25 ( 0.07, 0.90) | 0.25 ( 0.07, 0.89) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.7716 |
| Normal (<30) | 250 | 5 | 2.0 | 257 | 1 | 0.4 | 0.0936 | 0.19 ( 0.02, 1.65) | 0.19 ( 0.02, 1.65) | -0.02 (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 675 | 8 | 1.2 | 645 | 2 | 0.3 | 0.0668 | 0.26 ( 0.06, 1.23) | 0.26 ( 0.05, 1.23) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 260 | 0 | 0 | 261 | 0 | 0 | 0.9985 | 1.00 ( 0.02, 50.02) | 1.00 ( 0.02, 50.39) | 0.00 (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8636 |
| Low, moderate or high | 1018 | 12 | 1.2 | 1001 | 3 | 0.3 | 0.0215 | 0.25 ( 0.07, 0.90) | 0.25 ( 0.07, 0.90) | -0.01 (-0.02, 0.00) | |
| Very high | 167 | 1 | 0.6 | 162 | 0 | 0 | 0.4915 | 0.34 ( 0.01, 8.37) | 0.34 ( 0.01, 8.45) | -0.01 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.5060 |
| No | 205 | 2 | 1.0 | 211 | 1 | 0.5 | 0.5455 | 0.49 ( 0.04, 5.32) | 0.48 ( 0.04, 5.37) | -0.01 (-0.02, 0.01) | |
| Yes | 983 | 11 | 1.1 | 960 | 2 | 0.2 | 0.0138 | 0.19 ( 0.04, 0.84) | 0.18 ( 0.04, 0.83) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.9137 |
| No | 422 | 4 | 0.9 | 408 | 1 | 0.2 | 0.1909 | 0.26 ( 0.03, 2.30) | 0.26 ( 0.03, 2.31) | -0.01 (-0.02, 0.00) | |
| Yes | 766 | 9 | 1.2 | 763 | 2 | 0.3 | 0.0347 | 0.22 ( 0.05, 1.03) | 0.22 ( 0.05, 1.03) | -0.01 (-0.02, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 629 | 6 | 1.0 | 589 | 2 | 0.3 | | | | | |
| Yes | 559 | 7 | 1.3 | 582 | 1 | 0.2 | | | | | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Dyspnoea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 5 | 0.4 | 0.0941 | 0.42 ( 0.15, 1.20) | 0.42 ( 0.15, 1.20) | -0.01 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Osteoarthritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 8 | 0.7 | 0.2879 | 0.62 ( 0.26, 1.50) | 0.62 ( 0.26, 1.51) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 15 | 1.3 | 1171 | 6 | 0.5 | 0.0524 | 0.41 ( 0.16, 1.04) | 0.40 ( 0.16, 1.04) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Diabetic foot

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 13 | 1.1 | 1171 | 8 | 0.7 | 0.2879 | 0.62 ( 0.26, 1.50) | 0.62 ( 0.26, 1.51) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 7 | 0.6 | 0.2626 | 0.59 ( 0.23, 1.50) | 0.59 ( 0.23, 1.50) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 25 | 2.1 | 1171 | 13 | 1.1 | 0.0551 | 0.53 ( 0.27, 1.03) | 0.52 ( 0.27, 1.03) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 25 | 2.1 | 1171 | 22 | 1.9 | 0.6950 | 0.89 ( 0.51, 1.57) | 0.89 ( 0.50, 1.59) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 23 | 1.9 | 1171 | 17 | 1.5 | 0.3624 | 0.75 ( 0.40, 1.40) | 0.75 ( 0.40, 1.40) | 0.00 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina unstable

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 20 | 1.7 | 1171 | 14 | 1.2 | 0.3201 | 0.71 ( 0.36, 1.40) | 0.71 ( 0.36, 1.41) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 20 | 1.7 | 1171 | 10 | 0.9 | 0.0722 | 0.51 ( 0.24, 1.08) | 0.50 ( 0.23, 1.08) | -0.01 (-0.02, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Coronary artery disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 16 | 1.3 | 1171 | 13 | 1.1 | 0.6020 | 0.82 ( 0.40, 1.71) | 0.82 ( 0.39, 1.72) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 21 | 1.8 | 1171 | 20 | 1.7 | 0.9116 | 0.97 ( 0.53, 1.77) | 0.97 ( 0.52, 1.79) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Cerebrovascular accident

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 11 | 0.9 | 1171 | 13 | 1.1 | 0.6557 | 1.20 ( 0.54, 2.67) | 1.20 ( 0.54, 2.69) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypoglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 30 | 2.5 | 1171 | 22 | 1.9 | 0.2849 | 0.74 ( 0.43, 1.28) | 0.74 ( 0.42, 1.29) | -0.01 (-0.02, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 14 | 1.2 | 1171 | 12 | 1.0 | 0.7207 | 0.87 ( 0.40, 1.87) | 0.87 ( 0.40, 1.89) | 0.00 (-0.01, 0.01) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

Table R.4.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 1188 | 12 | 1.0 | 1171 | 7 | 0.6 | 0.2626 | 0.59 ( 0.23, 1.50) | 0.59 ( 0.23, 1.50) | 0.00 (-0.01, 0.00) | |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 18.0. * Chi-square test for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction).

**R.4.2.6**

R.4.2.6 Medical concepts for adverse events of special interest and other specific AEs

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code Scope | Preferred term code | Preferred term |
|---|---|---|---|---|
| All events of sub-BIcMQ 'Pyelonephritis', all events of PT 'Urosepsis' | Pylenophritis or Urosepsis (BIcMQ) | 0000000101 | 10023424 | Kidney infection |
| | | | 10034531 | Perinephric abscess |
| | | | 10037596 | Pyelonephritis |
| | | | 10037597 | Pyelonephritis acute |
| | | | 10037601 | Pyelonephritis chronic |
| | | | 10037603 | Pyelonephritis mycoplasmal |
| | | | 10037653 | Pyonephrosis |
| | | | 10038351 | Renal abscess |
| | | | 10048709 | Urosepsis |
| | | | 10049100 | Pyelocystitis |
| | | | 10058596 | Renal cyst infection |
| | | | 10059517 | Bacterial pyelonephritis |
| | | | 10065213 | Pyelonephritis viral |
| | | | 10065214 | Pyelonephritis fungal |
| | | | 10068822 | Emphysematous pyelonephritis |
| | | | 10074409 | Escherichia pyelonephritis |
| BIcMQ 'Bone fractures' | Bone fracture events (BIcMQ) | 0000000006 | 10000397 | Acetabulum fracture |
| | | | 10002544 | Ankle fracture |
| | | | 10009245 | Clavicle fracture |
| | | | 10010149 | Complicated fracture |
| | | | 10010214 | Compression fracture |
| | | | 10014487 | Elevation skull fracture |
| | | | 10016042 | Facial bones fracture |
| | | | 10016450 | Femoral neck fracture |
| | | | 10016454 | Femur fracture |
| | | | 10016667 | Fibula fracture |
| | | | 10016970 | Foot fracture |
| | | | 10016997 | Forearm fracture |
| | | | 10017076 | Fracture |
| | | | 10017290 | Fractured ischium |
| | | | 10017308 | Fractured sacrum |
| | | | 10017310 | Fractured skull depressed |
| | | | 10018720 | Greenstick fracture |
| | | | 10019114 | Hand fracture |
| | | | 10020100 | Hip fracture |
| | | | 10020462 | Humerus fracture |
| | | | 10021343 | Ilium fracture |
| | | | 10023149 | Jaw fracture |
| | | | 10028200 | Multiple fractures |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| BIcMQ 'Bone fractures' | Bone fracture events (BIcMQ) | 0000000006 | | 10030527 | Open fracture |
| | | | | 10031290 | Osteoporotic fracture |
| | | | | 10034122 | Patella fracture |
| | | | | 10034156 | Pathological fracture |
| | | | | 10037802 | Radius fracture |
| | | | | 10039117 | Rib fracture |
| | | | | 10039579 | Scapula fracture |
| | | | | 10040960 | Skull fractured base |
| | | | | 10041541 | Spinal compression fracture |
| | | | | 10041569 | Spinal fracture |
| | | | | 10042015 | Sternal fracture |
| | | | | 10042212 | Stress fracture |
| | | | | 10043827 | Tibia fracture |
| | | | | 10045375 | Ulna fracture |
| | | | | 10048049 | Wrist fracture |
| | | | | 10049164 | Fractured coccyx |
| | | | | 10049514 | Traumatic fracture |
| | | | | 10049946 | Cervical vertebral fracture |
| | | | | 10049947 | Lumbar vertebral fracture |
| | | | | 10049948 | Thoracic vertebral fracture |
| | | | | 10052614 | Comminuted fracture |
| | | | | 10053962 | Epiphyseal fracture |
| | | | | 10061161 | Pelvic fracture |
| | | | | 10061365 | Skull fracture |
| | | | | 10061394 | Upper limb fracture |
| | | | | 10061599 | Lower limb fracture |
| | | | | 10062544 | Tooth fracture |
| | | | | 10066094 | Torus fracture |
| | | | | 10066184 | Avulsion fracture |
| | | | | 10066386 | Impacted fracture |
| | | | | 10069135 | Periprosthetic fracture |
| | | | | 10070286 | Pubis fracture |
| | | | | 10070884 | Atypical femur fracture |
| | | | | 10072132 | Fracture pain |
| | | | | 10072395 | Atypical fracture |
| | | | | 10073162 | Chance fracture |
| | | | | 10073853 | Osteochondral fracture |
| | | | | 10074362 | Sacroiliac fracture |
| | | | | 10074551 | Limb fracture |
| BIcMQ 'Diabetic ketoacidosis' | Ketoacidosis (BIcMQ) | 0000000040 | | 10012671 | Diabetic ketoacidosis |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| BIcMQ 'Diabetic ketoacidosis' | Ketoacidosis (BIcMQ) | 0000000040 | | 10012672 | Diabetic ketoacidotic hyperglycaemic coma |
| | | | | 10023379 | Ketoacidosis |
| BIcMQ 'Genital infections' | Genital infections (BIcMQ) | 0000000001 | | 10004055 | Bacterial vaginosis |
| | | | | 10004074 | Balanitis candida |
| | | | | 10004078 | Balanoposthitis |
| | | | | 10004138 | Bartholin's abscess |
| | | | | 10004142 | Bartholinitis |
| | | | | 10008323 | Cervicitis |
| | | | | 10008325 | Cervicitis cystic |
| | | | | 10014791 | Endometritis |
| | | | | 10015000 | Epididymitis |
| | | | | 10018143 | Genital candidiasis |
| | | | | 10020497 | Hydrocele male infected |
| | | | | 10030345 | Oophoritis |
| | | | | 10031064 | Orchitis |
| | | | | 10033119 | Ovarian abscess |
| | | | | 10033847 | Parametritis |
| | | | | 10034236 | Pelvic abscess |
| | | | | 10034254 | Pelvic inflammatory disease |
| | | | | 10034256 | Pelvic inflammatory disease mycoplasmal |
| | | | | 10034294 | Penile abscess |
| | | | | 10036934 | Prostatic abscess |
| | | | | 10036978 | Prostatitis |
| | | | | 10037651 | Pyometra |
| | | | | 10039453 | Salpingitis |
| | | | | 10039748 | Scrotal gangrene |
| | | | | 10039954 | Seminal vesiculitis |
| | | | | 10044250 | Toxic shock syndrome staphylococcal |
| | | | | 10044251 | Toxic shock syndrome streptococcal |
| | | | | 10046914 | Vaginal infection |
| | | | | 10046957 | Vaginitis gardnerella |
| | | | | 10047732 | Vulval abscess |
| | | | | 10047752 | Vulval cellulitis |
| | | | | 10047780 | Vulvitis |
| | | | | 10047784 | Vulvovaginal candidiasis |
| | | | | 10047794 | Vulvovaginitis |
| | | | | 10048461 | Genital infection |
| | | | | 10049205 | Clitoris abscess |
| | | | | 10049571 | Scrotal abscess |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| BIcMQ 'Genital infections' | Genital infections (BIcMQ) | 0000000001 | | 10049573 | Vaginal abscess |
| | | | | 10049677 | Salpingo-oophoritis |
| | | | | 10050428 | Fallopian tube abscess |
| | | | | 10050662 | Prostate infection |
| | | | | 10050739 | Erosive balanitis |
| | | | | 10051458 | Myometritis |
| | | | | 10051483 | Prostatovesiculitis |
| | | | | 10052301 | Vaginal cellulitis |
| | | | | 10052457 | Perineal abscess |
| | | | | 10054259 | Escherichia vaginitis |
| | | | | 10054824 | Tubo-ovarian abscess |
| | | | | 10056254 | Intrauterine infection |
| | | | | 10056345 | Rectovaginal septum abscess |
| | | | | 10056628 | Ovarian bacterial infection |
| | | | | 10057001 | Seminal vesicular infection |
| | | | | 10058674 | Pelvic infection |
| | | | | 10058682 | Vaginitis viral |
| | | | | 10059070 | Pelvic sepsis |
| | | | | 10061179 | Genital infection bacterial |
| | | | | 10061180 | Genital infection fungal |
| | | | | 10061182 | Genitourinary tract infection |
| | | | | 10061912 | Penile infection |
| | | | | 10061977 | Genital infection female |
| | | | | 10062156 | Scrotal infection |
| | | | | 10062167 | Vaginitis bacterial |
| | | | | 10062233 | Uterine infection |
| | | | | 10062316 | Genital abscess |
| | | | | 10062521 | Genital infection male |
| | | | | 10062707 | Parametric abscess |
| | | | | 10063012 | Uterine abscess |
| | | | | 10064501 | Spermatic cord funiculitis |
| | | | | 10064724 | Testicular abscess |
| | | | | 10064899 | Vulvovaginal mycotic infection |
| | | | | 10064929 | Cellulitis of male external genital organ |
| | | | | 10065222 | Genital infection viral |
| | | | | 10065582 | Urogenital infection fungal |
| | | | | 10065583 | Urogenital infection bacterial |
| | | | | 10066416 | Vulvovaginal human papilloma virus infection |
| | | | | 10066876 | Perineal infection |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| BIcMQ 'Genital infections' | Genital infections (BIcMQ) | 0000000001 | | 10067185 | Vulvovaginitis streptococcal |
| | | | | 10067236 | Cervicitis streptococcal |
| | | | | 10067320 | Prostatitis Escherichia coli |
| | | | | 10067741 | Balanoposthitis infective |
| | | | | 10068682 | Gangrenous balanitis |
| | | | | 10069918 | Bacterial prostatitis |
| | | | | 10071209 | Candida cervicitis |
| | | | | 10072020 | Pyospermia |
| | | | | 10072210 | Genital herpes zoster |
| | | | | 10074861 | Endometritis bacterial |
| | | | | 10074997 | Mycoplasma genitalium infection |
| | | | | 10075062 | Cervicitis mycoplasmal |
| BIcMQ 'Hypoglycaemic events' | Hypoglycaemic events (BIcMQ) | 0000000007 | | 10005555 | Blood glucose decreased |
| | | | | 10020993 | Hypoglycaemia |
| | | | | 10020994 | Hypoglycaemia neonatal |
| | | | | 10020997 | Hypoglycaemia unawareness |
| | | | | 10021000 | Hypoglycaemic coma |
| | | | | 10021002 | Hypoglycaemic encephalopathy |
| | | | | 10040576 | Shock hypoglycaemic |
| | | | | 10048803 | Hypoglycaemic seizure |
| | | | | 10054998 | Neuroglycopenia |
| | | | | 10060378 | Hyperinsulinaemia |
| | | | | 10061211 | Hyperinsulinism |
| | | | | 10065981 | Hypoglycaemic unconsciousness |
| BIcMQ 'Volume depletion' | Volume depletion events (BIcMQ) | 0000000005 | | 10005731 | Blood pressure ambulatory decreased |
| | | | | 10005734 | Blood pressure decreased |
| | | | | 10005758 | Blood pressure systolic decreased |
| | | | | 10012174 | Dehydration |
| | | | | 10021097 | Hypotension |
| | | | | 10021137 | Hypovolaemia |
| | | | | 10031127 | Orthostatic hypotension |
| | | | | 10042772 | Syncope |
| Narrow BIcMQ 'Urinary tract infection' | Urinary tract infections (BIcMQ) | 0000000002 | | 10004056 | Bacteriuria |
| | | | | 10004058 | Bacteriuria in pregnancy |
| | | | | 10011781 | Cystitis |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Urinary tract infection' | Urinary tract infections (BIcMQ) | 0000000002 | | 10011790 | Cystitis escherichia |
| | | | | 10011792 | Cystitis gonococcal |
| | | | | 10011793 | Cystitis haemorrhagic |
| | | | | 10011797 | Cystitis klebsiella |
| | | | | 10011799 | Cystitis pseudomonal |
| | | | | 10017525 | Fungal cystitis |
| | | | | 10018185 | Genitourinary chlamydia infection |
| | | | | 10023424 | Kidney infection |
| | | | | 10029117 | Nephritis |
| | | | | 10034531 | Perinephric abscess |
| | | | | 10037596 | Pyelonephritis |
| | | | | 10037597 | Pyelonephritis acute |
| | | | | 10037601 | Pyelonephritis chronic |
| | | | | 10037603 | Pyelonephritis mycoplasmal |
| | | | | 10037653 | Pyonephrosis |
| | | | | 10038351 | Renal abscess |
| | | | | 10038530 | Renal syphilis |
| | | | | 10038534 | Renal tuberculosis |
| | | | | 10044758 | Tuberculosis bladder |
| | | | | 10044828 | Tuberculosis of genitourinary system |
| | | | | 10045026 | Tuberculosis ureter |
| | | | | 10046424 | Urethral abscess |
| | | | | 10046462 | Urethral papilloma |
| | | | | 10046470 | Urethral stricture post infection |
| | | | | 10046480 | Urethritis |
| | | | | 10046482 | Urethritis chlamydial |
| | | | | 10046483 | Urethritis gonococcal |
| | | | | 10046489 | Urethritis trichomonal |
| | | | | 10046490 | Urethritis ureaplasmal |
| | | | | 10046571 | Urinary tract infection |
| | | | | 10046572 | Urinary tract infection enterococcal |
| | | | | 10046573 | Urinary tract infection neonatal |
| | | | | 10046704 | Urogenital trichomoniasis |
| | | | | 10048709 | Urosepsis |
| | | | | 10048837 | Cystitis glandularis |
| | | | | 10049059 | Urinary tract infection fungal |
| | | | | 10049100 | Pyelocystitis |
| | | | | 10050762 | Candiduria |
| | | | | 10051250 | Ureteritis |
| | | | | 10051350 | Cytomegalovirus urinary tract infection |
| | | | | 10051959 | Urinary bladder abscess |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Urinary tract infection' | Urinary tract infections (BIcMQ) | 0000000002 | | 10052238 | Escherichia urinary tract infection |
| | | | | 10052299 | Urethral carbuncle |
| | | | | 10054088 | Urinary tract infection bacterial |
| | | | | 10056351 | Emphysematous cystitis |
| | | | | 10056396 | Asymptomatic bacteriuria |
| | | | | 10057373 | Adenoviral haemorrhagic cystitis |
| | | | | 10058523 | Bladder candidiasis |
| | | | | 10058596 | Renal cyst infection |
| | | | | 10059346 | Viral haemorrhagic cystitis |
| | | | | 10059517 | Bacterial pyelonephritis |
| | | | | 10061181 | Genitourinary tract gonococcal infection |
| | | | | 10061182 | Genitourinary tract infection |
| | | | | 10061395 | Ureter abscess |
| | | | | 10062279 | Urinary tract infection pseudomonal |
| | | | | 10062280 | Urinary tract infection staphylococcal |
| | | | | 10064825 | Urinary tract infection viral |
| | | | | 10064850 | Cystitis erosive |
| | | | | 10065197 | Cystitis viral |
| | | | | 10065198 | Cystitis bacterial |
| | | | | 10065199 | Cystitis helminthic |
| | | | | 10065213 | Pyelonephritis viral |
| | | | | 10065214 | Pyelonephritis fungal |
| | | | | 10065381 | Polyomavirus-associated nephropathy |
| | | | | 10065582 | Urogenital infection fungal |
| | | | | 10065583 | Urogenital infection bacterial |
| | | | | 10066757 | Urinary tract abscess |
| | | | | 10068822 | Emphysematous pyelonephritis |
| | | | | 10070300 | Streptococcal urinary tract infection |
| | | | | 10070737 | HIV associated nephropathy |
| | | | | 10071736 | Acute focal bacterial nephritis |
| | | | | 10072058 | Perinephritis |
| | | | | 10074409 | Escherichia pyelonephritis |
| | | | | 10074457 | Bladder diverticulitis |
| | | | | 10074997 | Mycoplasma genitalium infection |
| | | | | 10075063 | Urethritis mycoplasmal |
| Narrow SMQ 'Acute renal failure' | Acute renal failure (SMQ) | 20000003 | Narrow | 10001017 | Acute prerenal failure |
| | | | | 10002847 | Anuria |
| | | | | 10003885 | Azotaemia |
| | | | | 10018875 | Haemodialysis |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQ 'Acute renal failure' | Acute renal failure (SMQ) | 20000003 | Narrow | 10029155 | Nephropathy toxic |
| | | | | 10030302 | Oliguria |
| | | | | 10034660 | Peritoneal dialysis |
| | | | | 10038435 | Renal failure |
| | | | | 10038447 | Renal failure neonatal |
| | | | | 10049776 | Renal impairment neonatal |
| | | | | 10049778 | Neonatal anuria |
| | | | | 10053090 | Haemofiltration |
| | | | | 10061105 | Dialysis |
| | | | | 10062237 | Renal impairment |
| | | | | 10066338 | Continuous haemodiafiltration |
| | | | | 10069339 | Acute kidney injury |
| | | | | 10069688 | Acute phosphate nephropathy |
| | | | | 10072370 | Prerenal failure |
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | Narrow | 10000804 | Acute hepatic failure |
| | | | | 10001547 | Alanine aminotransferase abnormal |
| | | | | 10001551 | Alanine aminotransferase increased |
| | | | | 10001942 | Ammonia abnormal |
| | | | | 10001946 | Ammonia increased |
| | | | | 10003445 | Ascites |
| | | | | 10003477 | Aspartate aminotransferase abnormal |
| | | | | 10003481 | Aspartate aminotransferase increased |
| | | | | 10003547 | Asterixis |
| | | | | 10003827 | Autoimmune hepatitis |
| | | | | 10004659 | Biliary cirrhosis |
| | | | | 10004661 | Biliary cirrhosis primary |
| | | | | 10004664 | Biliary fibrosis |
| | | | | 10004685 | Bilirubin conjugated increased |
| | | | | 10004792 | Biopsy liver abnormal |
| | | | | 10005364 | Blood bilirubin increased |
| | | | | 10005370 | Blood bilirubin unconjugated increased |
| | | | | 10006408 | Bromosulphthalein test abnormal |
| | | | | 10008635 | Cholestasis |
| | | | | 10008909 | Chronic hepatitis |
| | | | | 10010075 | Coma hepatic |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | Narrow | 10017688 | Gamma-glutamyltransferase abnormal |
| | | | | 10017693 | Gamma-glutamyltransferase increased |
| | | | | 10019621 | Hepaplastin abnormal |
| | | | | 10019622 | Hepaplastin decreased |
| | | | | 10019637 | Hepatic atrophy |
| | | | | 10019641 | Hepatic cirrhosis |
| | | | | 10019645 | Hepatic congestion |
| | | | | 10019660 | Hepatic encephalopathy |
| | | | | 10019663 | Hepatic failure |
| | | | | 10019668 | Hepatic fibrosis |
| | | | | 10019670 | Hepatic function abnormal |
| | | | | 10019692 | Hepatic necrosis |
| | | | | 10019705 | Hepatic pain |
| | | | | 10019708 | Hepatic steatosis |
| | | | | 10019717 | Hepatitis |
| | | | | 10019727 | Hepatitis acute |
| | | | | 10019754 | Hepatitis cholestatic |
| | | | | 10019755 | Hepatitis chronic active |
| | | | | 10019759 | Hepatitis chronic persistent |
| | | | | 10019772 | Hepatitis fulminant |
| | | | | 10019795 | Hepatitis toxic |
| | | | | 10019837 | Hepatocellular injury |
| | | | | 10019842 | Hepatomegaly |
| | | | | 10019845 | Hepatorenal failure |
| | | | | 10019846 | Hepatorenal syndrome |
| | | | | 10019847 | Hepatosplenomegaly |
| | | | | 10019851 | Hepatotoxicity |
| | | | | 10020575 | Hyperammonaemia |
| | | | | 10020578 | Hyperbilirubinaemia |
| | | | | 10021209 | Icterus index increased |
| | | | | 10023025 | Ischaemic hepatitis |
| | | | | 10023126 | Jaundice |
| | | | | 10023129 | Jaundice cholestatic |
| | | | | 10023136 | Jaundice hepatocellular |
| | | | | 10023321 | Kayser-Fleischer ring |
| | | | | 10024670 | Liver disorder |
| | | | | 10024690 | Liver function test abnormal |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | Narrow | 10024712 | Liver tenderness |
| | | | | 10024714 | Liver transplant |
| | | | | 10025129 | Lupoid hepatic cirrhosis |
| | | | | 10030210 | Oesophageal varices haemorrhage |
| | | | | 10036200 | Portal hypertension |
| | | | | 10039012 | Reye's syndrome |
| | | | | 10045428 | Ultrasound liver abnormal |
| | | | | 10048611 | Cholaemia |
| | | | | 10049631 | Oedema due to hepatic disease |
| | | | | 10050792 | Urine bilirubin increased |
| | | | | 10050897 | Portal hypertensive gastropathy |
| | | | | 10051010 | Duodenal varices |
| | | | | 10051012 | Gastric varices |
| | | | | 10051015 | Radiation hepatitis |
| | | | | 10051081 | Nodular regenerative hyperplasia |
| | | | | 10051333 | Guanase increased |
| | | | | 10051343 | Bile output decreased |
| | | | | 10051344 | Bile output abnormal |
| | | | | 10051924 | Hypercholia |
| | | | | 10052274 | Hepatopulmonary syndrome |
| | | | | 10052279 | Renal and liver transplant |
| | | | | 10052280 | Liver and small intestine transplant |
| | | | | 10052550 | Liver induration |
| | | | | 10052554 | Foetor hepaticus |
| | | | | 10053219 | Non-alcoholic steatohepatitis |
| | | | | 10053244 | Hepatocellular foamy cell syndrome |
| | | | | 10054125 | Perihepatic discomfort |
| | | | | 10054889 | Transaminases increased |
| | | | | 10056091 | Varices oesophageal |
| | | | | 10056536 | X-ray hepatobiliary abnormal |
| | | | | 10056956 | Subacute hepatic failure |
| | | | | 10057110 | Hepatic mass |
| | | | | 10057572 | Gastric varices haemorrhage |
| | | | | 10057573 | Chronic hepatic failure |
| | | | | 10058117 | Ocular icterus |
| | | | | 10058477 | Blood bilirubin abnormal |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | Narrow | 10059710 | Galactose elimination capacity test abnormal |
| | | | | 10059712 | Galactose elimination capacity test decreased |
| | | | | 10060794 | Hepatic enzyme decreased |
| | | | | 10060795 | Hepatic enzyme increased |
| | | | | 10061009 | Bilirubin excretion disorder |
| | | | | 10061947 | Liver scan abnormal |
| | | | | 10061997 | Hepatectomy |
| | | | | 10061998 | Hepatic lesion |
| | | | | 10062000 | Hepatobiliary disease |
| | | | | 10062040 | Liver operation |
| | | | | 10062685 | Hepatic enzyme abnormal |
| | | | | 10062688 | Transaminases abnormal |
| | | | | 10063075 | Cryptogenic cirrhosis |
| | | | | 10064190 | Cholestatic pruritus |
| | | | | 10064558 | Total bile acids increased |
| | | | | 10064668 | Hepatic infiltration eosinophilic |
| | | | | 10064676 | Graft versus host disease in liver |
| | | | | 10064712 | Mitochondrial aspartate aminotransferase increased |
| | | | | 10065274 | Hepatic calcification |
| | | | | 10066195 | Hepatobiliary scan abnormal |
| | | | | 10066244 | Hepatic sequestration |
| | | | | 10066263 | Acute graft versus host disease in liver |
| | | | | 10066599 | Hepatic encephalopathy prophylaxis |
| | | | | 10066758 | Mixed liver injury |
| | | | | 10066869 | Molar ratio of total branched-chain amino acid to tyrosine |
| | | | | 10067125 | Liver injury |
| | | | | 10067281 | Portopulmonary hypertension |
| | | | | 10067338 | Retrograde portal vein flow |
| | | | | 10067365 | Hepatic hydrothorax |
| | | | | 10067718 | Bilirubin conjugated abnormal |
| | | | | 10067737 | Lupus hepatitis |
| | | | | 10067823 | Splenic varices |
| | | | | 10067969 | Cholestatic liver injury |
| | | | | 10068237 | Hypertransaminasaemia |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | Narrow | 10068287 | Child-Pugh-Turcotte score increased |
| | | | | 10068358 | Hepatic vascular resistance increased |
| | | | | 10068547 | Bacterascites |
| | | | | 10068662 | Splenic varices haemorrhage |
| | | | | 10068923 | Portal hypertensive enteropathy |
| | | | | 10068997 | Hepatic artery flow decreased |
| | | | | 10070815 | Acute yellow liver atrophy |
| | | | | 10070953 | Reynold's syndrome |
| | | | | 10071198 | Allergic hepatitis |
| | | | | 10071265 | Diabetic hepatopathy |
| | | | | 10071502 | Intestinal varices |
| | | | | 10072160 | Chronic graft versus host disease in liver |
| | | | | 10072268 | Drug-induced liver injury |
| | | | | 10072284 | Varicose veins of abdominal wall |
| | | | | 10072319 | Gallbladder varices |
| | | | | 10073209 | Portal vein dilatation |
| | | | | 10073215 | Peripancreatic varices |
| | | | | 10073979 | Portal vein cavernous transformation |
| | | | | 10074150 | Biliary ascites |
| | | | | 10074151 | Parenteral nutrition associated liver disease |
| | | | | 10074726 | Portal fibrosis |
| | | | | 10075895 | Liver palpable |
| | | | | 10076204 | Minimal hepatic encephalopathy |
| | | | | 10076215 | Computerised tomogram liver |
| | | | | 10076237 | Gastric variceal injection |
| | | | | 10076238 | Gastric variceal ligation |
| | | | | 10076254 | Hepatic hypertrophy |
| | | | | 10076331 | Steatohepatitis |
| PTs 'Blood Potassium increased', 'Hyperkalaemia' | Hyperkalaemia (user-defined) | 40000021 | | 10005725 | Blood potassium increased |
| | | | | 10020646 | Hyperkalaemia |
| PTs 'Gout', 'Gouty arthritis', 'Gouty tophus' | Gout (user-defined) | 40000032 | | 10018627 | Gout |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

Listing R.4.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| PTs 'Gout', 'Gouty arthritis', 'Gouty tophus' | Gout (user-defined) | 40000032 | | 10018634 | Gouty arthritis |
| | | | | 10018641 | Gouty tophus |

Analyses are based on 1245.25 CKD subpopulation (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 18.0

**R.5**

R.5 Analyses of pooled 1245.110 and 1245.121 - CKD subpopulation

**R.5.1**

**R.5.1.1**

**R.5.1.1.1**

R.5.1.1.1.1.1 Time to all-cause mortality

**Figure R.5.1.1.1.1: 1**

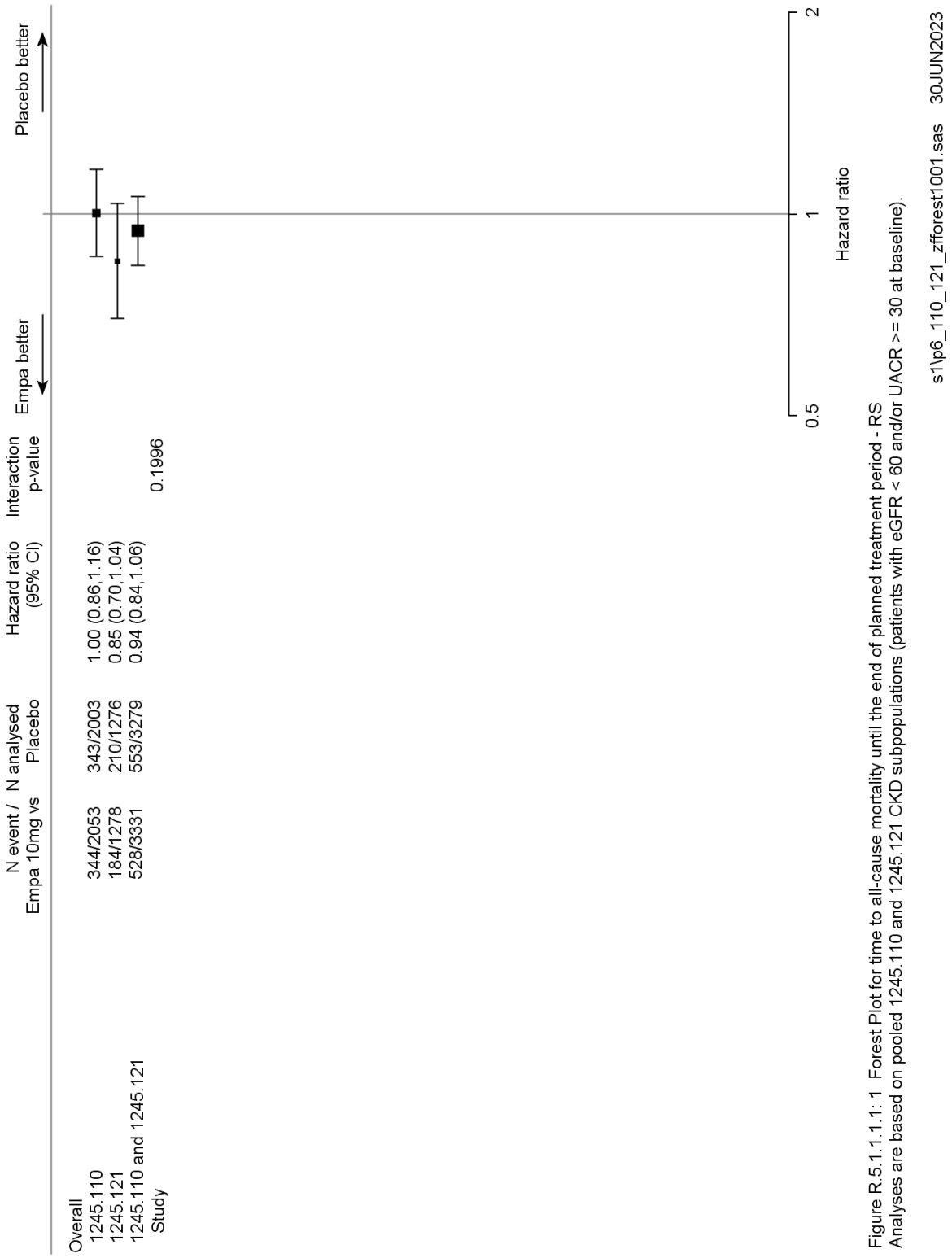


Figure R.5.1.1.1.1: 1 Forest Plot for time to all-cause mortality until the end of planned treatment period - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.1.1: 1 Cox Regression for time to all-cause mortality until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 553 | 16.9 | 9.33 | 3331 | 528 | 15.9 | 8.76 | 0.94 | (0.84,1.06) | 0.3271 | |
| Study | | | | | | | | | | | | 0.1996 |
| Sex | | | | | | | | | | | | 0.9872 |
| Male | 2024 | 370 | 18.3 | 10.51 | 2069 | 360 | 17.4 | 10.01 | 0.94 | (0.82,1.09) | 0.4258 | |
| Female | 1255 | 183 | 14.6 | 7.59 | 1262 | 168 | 13.3 | 6.92 | 0.94 | (0.76,1.16) | 0.5680 | |
| Age [years] | | | | | | | | | | | | 0.9611 |
| <65 | 767 | 103 | 13.4 | 7.94 | 705 | 86 | 12.2 | 7.28 | 0.93 | (0.70,1.24) | 0.6421 | |
| >=65 | 2512 | 450 | 17.9 | 9.71 | 2626 | 442 | 16.8 | 9.12 | 0.94 | (0.83,1.07) | 0.3698 | |
| Region | | | | | | | | | | | | 0.8427 |
| North America | 434 | 73 | 16.8 | 8.60 | 433 | 79 | 18.2 | 9.36 | 1.01 | (0.74,1.40) | 0.9296 | |
| Latin America | 931 | 179 | 19.2 | 11.79 | 944 | 180 | 19.1 | 11.82 | 1.00 | (0.81,1.23) | 0.9978 | |
| Europe | 1338 | 220 | 16.4 | 8.80 | 1361 | 196 | 14.4 | 7.69 | 0.89 | (0.73,1.08) | 0.2385 | |
| Asia | 405 | 50 | 12.3 | 6.71 | 413 | 42 | 10.2 | 5.38 | 0.81 | (0.54,1.23) | 0.3252 | |
| Other | 171 | 31 | 18.1 | 9.76 | 180 | 31 | 17.2 | 9.41 | 1.01 | (0.61,1.66) | 0.9723 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.7544 |
| Diabetic | 1742 | 315 | 18.1 | 9.97 | 1780 | 305 | 17.1 | 9.54 | 0.96 | (0.82,1.12) | 0.5891 | |
| Non-Diabetic | 1537 | 238 | 15.5 | 8.59 | 1551 | 223 | 14.4 | 7.89 | 0.92 | (0.77,1.11) | 0.3797 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1262 |
| <30 | 1977 | 369 | 18.7 | 10.74 | 1930 | 313 | 16.2 | 9.23 | 0.88 | (0.76,1.03) | 0.1032 | |
| >=30 | 1302 | 184 | 14.1 | 7.38 | 1401 | 215 | 15.3 | 8.16 | 1.07 | (0.88,1.30) | 0.4972 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.9256 |
| <130 | 1686 | 288 | 17.1 | 10.10 | 1687 | 270 | 16.0 | 9.40 | 0.94 | (0.79,1.11) | 0.4456 | |
| >=130 | 1593 | 265 | 16.6 | 8.61 | 1644 | 258 | 15.7 | 8.18 | 0.95 | (0.80,1.13) | 0.5425 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7618 |
| <75 | 1656 | 306 | 18.5 | 10.45 | 1613 | 274 | 17.0 | 9.61 | 0.93 | (0.79,1.10) | 0.3875 | |
| 75 to <85 | 1006 | 156 | 15.5 | 8.37 | 1085 | 168 | 15.5 | 8.46 | 1.01 | (0.81,1.25) | 0.9469 | |
| >=85 | 617 | 91 | 14.7 | 8.01 | 633 | 86 | 13.6 | 7.24 | 0.89 | (0.66,1.19) | 0.4244 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.1.1: 1 Cox Regression for time to all-cause mortality until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1291 |
| <30 | 251 | 81 | 32.3 | 19.66 | 263 | 64 | 24.3 | 14.16 | 0.70 | (0.50,0.97) | 0.0336 | |
| 30 to <45 | 899 | 148 | 16.5 | 9.04 | 909 | 150 | 16.5 | 9.16 | 1.06 | (0.84,1.33) | 0.6349 | |
| >=45 | 2128 | 324 | 15.2 | 8.35 | 2159 | 314 | 14.5 | 7.98 | 0.94 | (0.81,1.10) | 0.4562 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2903 |
| Normal (<30) | 1218 | 157 | 12.9 | 7.03 | 1243 | 158 | 12.7 | 6.89 | 0.99 | (0.79,1.23) | 0.9202 | |
| Microalbuminuria (30 to <=300) | 1549 | 286 | 18.5 | 10.34 | 1547 | 250 | 16.2 | 8.95 | 0.87 | (0.73,1.03) | 0.1041 | |
| Macroalbuminuria (>300) | 500 | 107 | 21.4 | 11.75 | 525 | 119 | 22.7 | 13.04 | 1.10 | (0.85,1.44) | 0.4543 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5529 |
| Low, moderate or high | 2432 | 358 | 14.7 | 8.09 | 2496 | 344 | 13.8 | 7.53 | 0.93 | (0.80,1.08) | 0.3192 | |
| Very high | 836 | 193 | 23.1 | 12.98 | 820 | 184 | 22.4 | 12.83 | 1.00 | (0.82,1.22) | 0.9949 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.4890 |
| No | 573 | 111 | 19.4 | 10.27 | 579 | 101 | 17.4 | 9.11 | 0.86 | (0.66,1.13) | 0.2896 | |
| Yes | 2706 | 442 | 16.3 | 9.12 | 2752 | 427 | 15.5 | 8.68 | 0.96 | (0.84,1.10) | 0.5603 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.7828 |
| No | 344 | 79 | 23.0 | 11.86 | 349 | 66 | 18.9 | 10.14 | 0.91 | (0.65,1.26) | 0.5526 | |
| Yes | 2935 | 474 | 16.1 | 9.01 | 2982 | 462 | 15.5 | 8.59 | 0.95 | (0.84,1.08) | 0.4469 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.5031 |
| No | 275 | 39 | 14.2 | 7.02 | 307 | 33 | 10.7 | 5.51 | 0.81 | (0.51,1.29) | 0.3699 | |
| Yes | 3004 | 514 | 17.1 | 9.56 | 3024 | 495 | 16.4 | 9.12 | 0.95 | (0.84,1.08) | 0.4442 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.1.1: 2**

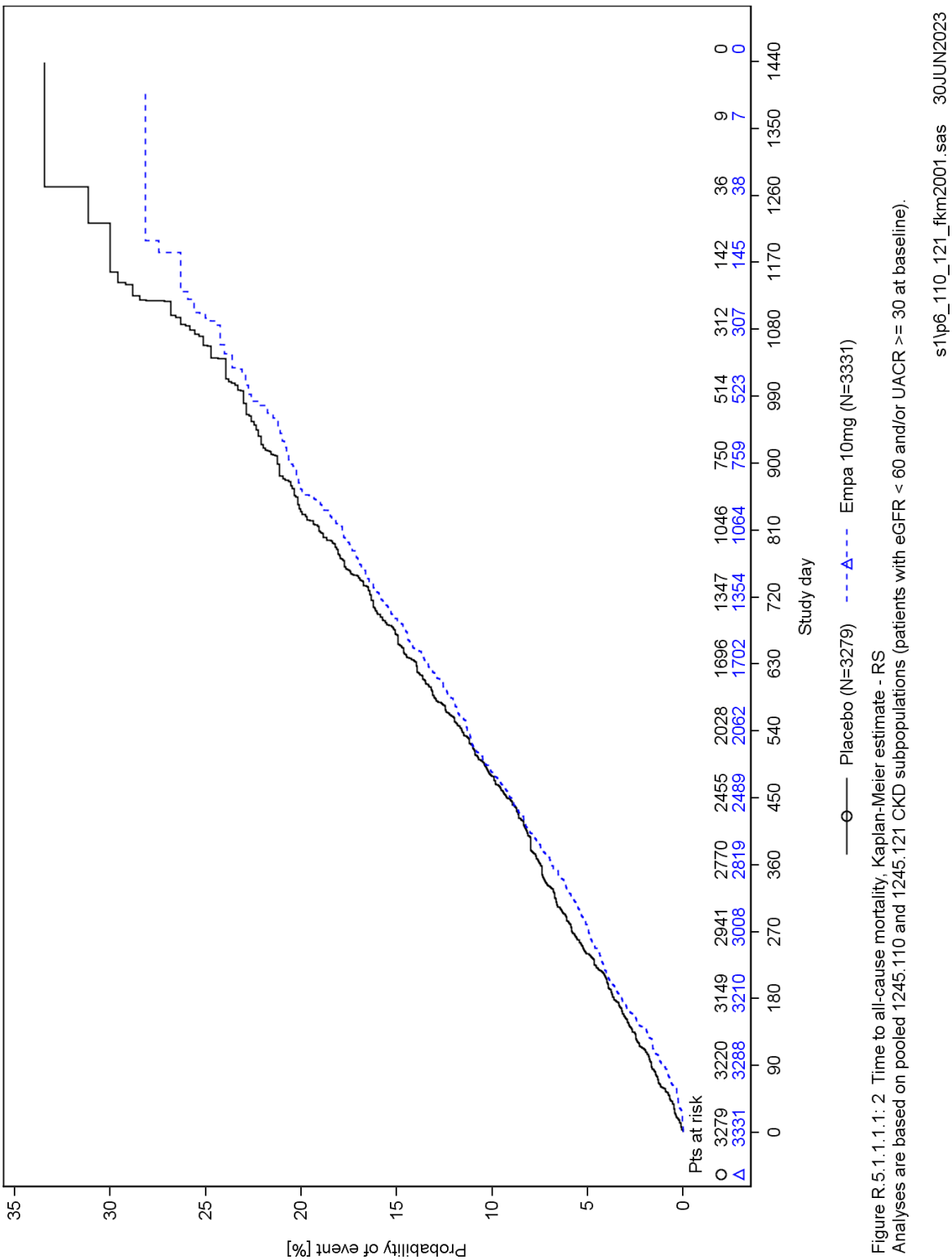


Figure R.5.1.1.1.1: 2 Time to all-cause mortality, Kaplan-Meier estimate - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.5.1.1.1.2**

R.5.1.1.1.2 Time to adjudicated CV death

**Figure R.5.1.1.1.2: 1**

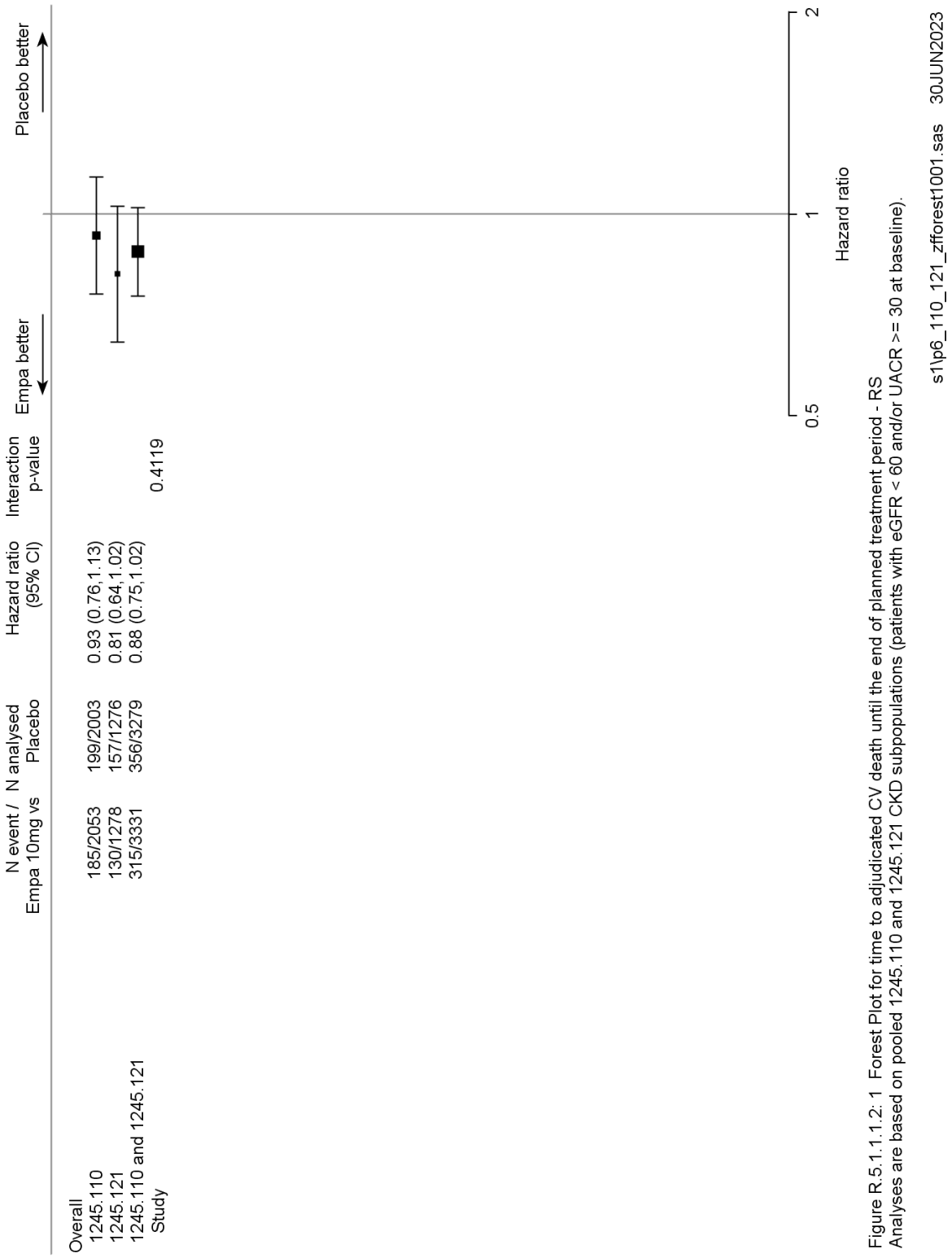


Figure R.5.1.1.1.2: 1 Forest Plot for time to adjudicated CV death until the end of planned treatment period - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.1.2: 1 Cox Regression for time to adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 356 | 10.9 | 6.00 | 3331 | 315 | 9.5 | 5.23 | 0.88 | (0.75,1.02) | 0.0903 | |
| Study | | | | | | | | | | | | 0.4119 |
| Sex | | | | | | | | | | | | 0.3499 |
| Male | 2024 | 232 | 11.5 | 6.59 | 2069 | 220 | 10.6 | 6.12 | 0.92 | (0.77,1.11) | 0.3899 | |
| Female | 1255 | 124 | 9.9 | 5.15 | 1262 | 95 | 7.5 | 3.91 | 0.79 | (0.60,1.03) | 0.0838 | |
| Age [years] | | | | | | | | | | | | 0.7494 |
| <65 | 767 | 72 | 9.4 | 5.55 | 705 | 59 | 8.4 | 5.00 | 0.92 | (0.65,1.30) | 0.6387 | |
| >=65 | 2512 | 284 | 11.3 | 6.13 | 2626 | 256 | 9.7 | 5.28 | 0.86 | (0.73,1.02) | 0.0926 | |
| Region | | | | | | | | | | | | 0.6935 |
| North America | 434 | 39 | 9.0 | 4.60 | 433 | 42 | 9.7 | 4.97 | 1.03 | (0.66,1.59) | 0.9100 | |
| Latin America | 931 | 114 | 12.2 | 7.51 | 944 | 111 | 11.8 | 7.29 | 0.97 | (0.74,1.26) | 0.8040 | |
| Europe | 1338 | 146 | 10.9 | 5.84 | 1361 | 116 | 8.5 | 4.55 | 0.80 | (0.63,1.02) | 0.0702 | |
| Asia | 405 | 39 | 9.6 | 5.23 | 413 | 29 | 7.0 | 3.71 | 0.73 | (0.45,1.18) | 0.1938 | |
| Other | 171 | 18 | 10.5 | 5.67 | 180 | 17 | 9.4 | 5.16 | 0.94 | (0.49,1.83) | 0.8584 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.6049 |
| Diabetic | 1742 | 197 | 11.3 | 6.23 | 1780 | 180 | 10.1 | 5.63 | 0.91 | (0.74,1.11) | 0.3506 | |
| Non-Diabetic | 1537 | 159 | 10.3 | 5.74 | 1551 | 135 | 8.7 | 4.77 | 0.84 | (0.67,1.05) | 0.1306 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2072 |
| <30 | 1977 | 244 | 12.3 | 7.10 | 1930 | 191 | 9.9 | 5.63 | 0.82 | (0.68,0.99) | 0.0422 | |
| >=30 | 1302 | 112 | 8.6 | 4.49 | 1401 | 124 | 8.9 | 4.70 | 1.01 | (0.78,1.30) | 0.9488 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7169 |
| <130 | 1686 | 190 | 11.3 | 6.66 | 1687 | 161 | 9.5 | 5.60 | 0.85 | (0.69,1.05) | 0.1409 | |
| >=130 | 1593 | 166 | 10.4 | 5.39 | 1644 | 154 | 9.4 | 4.88 | 0.90 | (0.73,1.13) | 0.3639 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.6784 |
| <75 | 1656 | 194 | 11.7 | 6.62 | 1613 | 170 | 10.5 | 5.96 | 0.92 | (0.75,1.13) | 0.4384 | |
| 75 to <85 | 1006 | 111 | 11.0 | 5.95 | 1085 | 95 | 8.8 | 4.78 | 0.80 | (0.60,1.05) | 0.1019 | |
| >=85 | 617 | 51 | 8.3 | 4.49 | 633 | 50 | 7.9 | 4.21 | 0.92 | (0.63,1.37) | 0.6949 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.1.2: 1 Cox Regression for time to adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.0792 |
| <30 | 251 | 44 | 17.5 | 10.68 | 263 | 32 | 12.2 | 7.08 | 0.64 | (0.41,1.01) | 0.0570 | |
| 30 to <45 | 899 | 87 | 9.7 | 5.31 | 909 | 95 | 10.5 | 5.80 | 1.13 | (0.84,1.51) | 0.4171 | |
| >=45 | 2128 | 225 | 10.6 | 5.80 | 2159 | 188 | 8.7 | 4.78 | 0.82 | (0.68,1.00) | 0.0491 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.1044 |
| Normal (<30) | 1218 | 99 | 8.1 | 4.44 | 1243 | 87 | 7.0 | 3.80 | 0.86 | (0.65,1.15) | 0.3148 | |
| Microalbuminuria (30 to <=300) | 1549 | 194 | 12.5 | 7.01 | 1547 | 152 | 9.8 | 5.44 | 0.79 | (0.64,0.98) | 0.0285 | |
| Macroalbuminuria (>300) | 500 | 61 | 12.2 | 6.70 | 525 | 75 | 14.3 | 8.22 | 1.21 | (0.87,1.70) | 0.2604 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.1975 |
| Low, moderate or high | 2432 | 241 | 9.9 | 5.45 | 2496 | 205 | 8.2 | 4.49 | 0.83 | (0.69,1.00) | 0.0461 | |
| Very high | 836 | 113 | 13.5 | 7.60 | 820 | 110 | 13.4 | 7.67 | 1.02 | (0.79,1.33) | 0.8684 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9866 |
| No | 573 | 66 | 11.5 | 6.11 | 579 | 60 | 10.4 | 5.41 | 0.87 | (0.62,1.24) | 0.4519 | |
| Yes | 2706 | 290 | 10.7 | 5.98 | 2752 | 255 | 9.3 | 5.19 | 0.88 | (0.74,1.04) | 0.1274 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3487 |
| No | 344 | 40 | 11.6 | 6.00 | 349 | 40 | 11.5 | 6.15 | 1.07 | (0.69,1.66) | 0.7614 | |
| Yes | 2935 | 316 | 10.8 | 6.00 | 2982 | 275 | 9.2 | 5.12 | 0.86 | (0.73,1.01) | 0.0592 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2810 |
| No | 275 | 28 | 10.2 | 5.04 | 307 | 19 | 6.2 | 3.17 | 0.64 | (0.36,1.15) | 0.1393 | |
| Yes | 3004 | 328 | 10.9 | 6.10 | 3024 | 296 | 9.8 | 5.45 | 0.90 | (0.77,1.05) | 0.1794 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.1.2: 2**

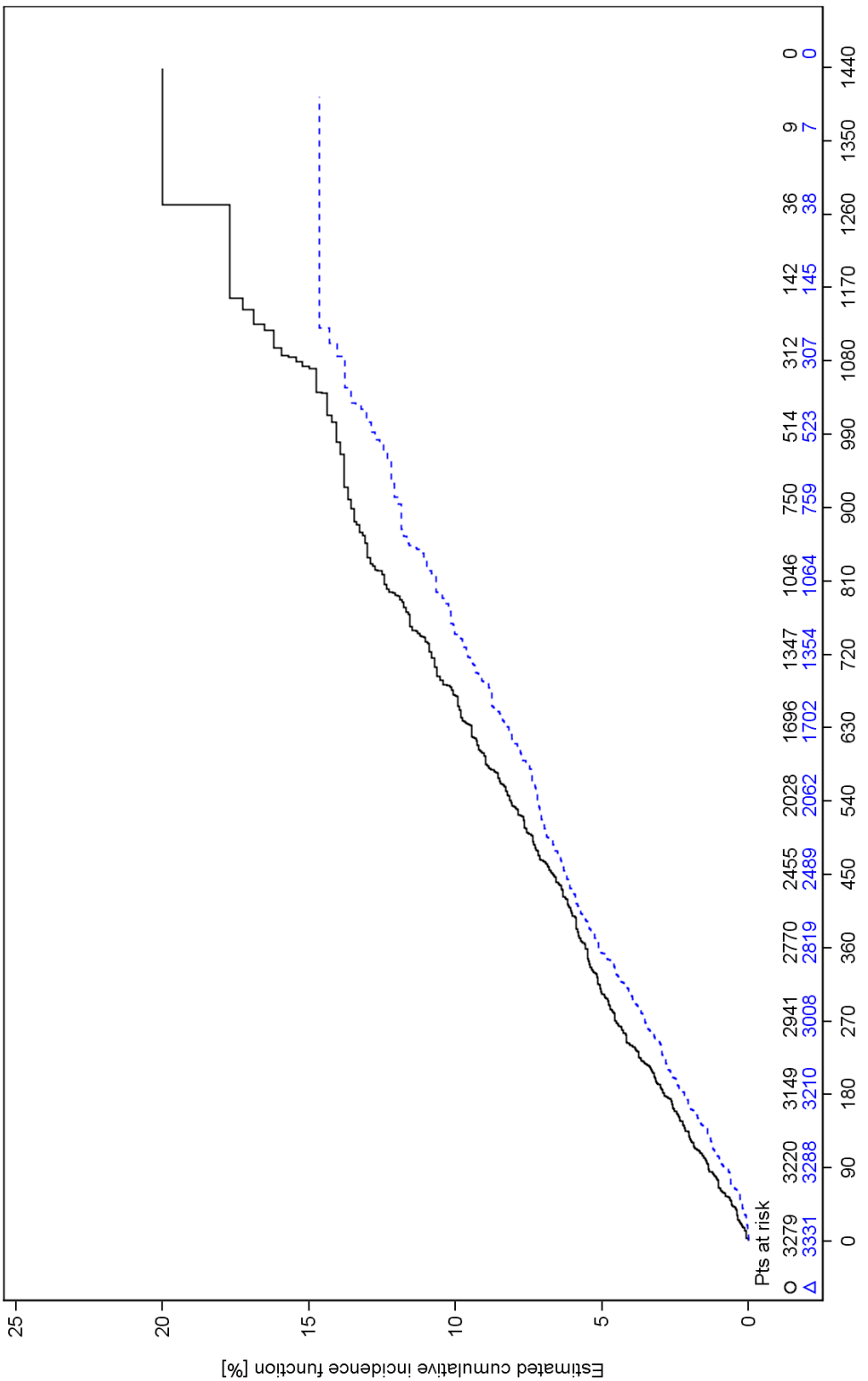


Figure R.5.1.1.1.2: 2 Time to adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.5.1.1.1.3**

R.5.1.1.1.3 Time to adjudicated renal death

**Figure R.5.1.1.1.3: 1**

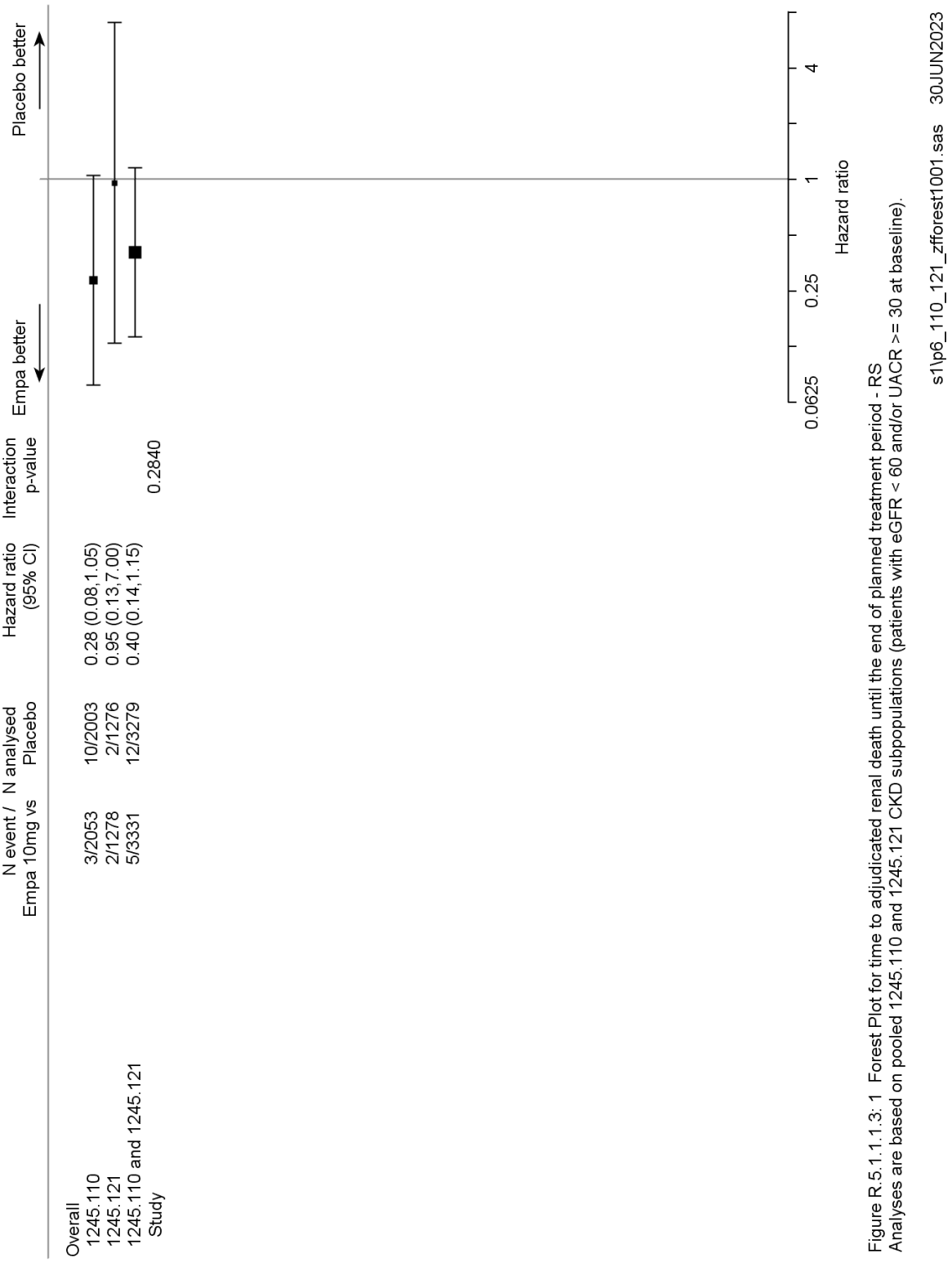


Figure R.5.1.1.1.3: 1 Forest Plot for time to adjudicated renal death until the end of planned treatment period - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.1.3: 1 Cox Regression for time to adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3279 | 12 | 0.4 | 0.20 | 3331 | 5 | 0.2 | 0.08 | 0.40 | (0.14, 1.15) | 0.0896 | |
| Study | | | | | | | | | | | | 0.2840 |
| Sex | | | | | | | | | | | | 0.4381 |
| Male | 2024 | 11 | 0.5 | 0.31 | 2069 | 4 | 0.2 | 0.11 | 0.34 | (0.11, 1.09) | 0.0694 | |
| Female | 1255 | 1 | 0.1 | 0.04 | 1262 | 1 | 0.1 | 0.04 | 1.13 | (0.07,18.08) | 0.9321 | |
| Age [years] | | | | | | | | | | | | |
| <65 | 767 | 6 | 0.8 | 0.46 | 705 | 3 | 0.4 | 0.25 | | | | |
| >=65 | 2512 | 6 | 0.2 | 0.13 | 2626 | 2 | 0.1 | 0.04 | | | | |
| Region | | | | | | | | | | | | |
| North America | 434 | 2 | 0.5 | 0.24 | 433 | 2 | 0.5 | 0.24 | | | | |
| Latin America | 931 | 5 | 0.5 | 0.33 | 944 | 1 | 0.1 | 0.07 | | | | |
| Europe | 1338 | 1 | 0.1 | 0.04 | 1361 | 1 | 0.1 | 0.04 | | | | |
| Asia | 405 | 1 | 0.2 | 0.13 | 413 | 0 | 0 | 0.00 | | | | |
| Other | 171 | 3 | 1.8 | 0.94 | 180 | 1 | 0.6 | 0.30 | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.8363 |
| Diabetic | 1742 | 9 | 0.5 | 0.28 | 1780 | 4 | 0.2 | 0.13 | 0.44 | (0.13, 1.44) | 0.1742 | |
| Non-Diabetic | 1537 | 3 | 0.2 | 0.11 | 1551 | 1 | 0.1 | 0.04 | 0.34 | (0.03, 3.24) | 0.3455 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9310 |
| <30 | 1977 | 8 | 0.4 | 0.23 | 1930 | 3 | 0.2 | 0.09 | 0.40 | (0.11, 1.50) | 0.1738 | |
| >=30 | 1302 | 4 | 0.3 | 0.16 | 1401 | 2 | 0.1 | 0.08 | 0.44 | (0.08, 2.41) | 0.3423 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.3095 |
| <130 | 1686 | 9 | 0.5 | 0.32 | 1687 | 2 | 0.1 | 0.07 | 0.26 | (0.05, 1.21) | 0.0853 | |
| >=130 | 1593 | 3 | 0.2 | 0.10 | 1644 | 3 | 0.2 | 0.10 | 0.82 | (0.16, 4.10) | 0.8078 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 1656 | 7 | 0.4 | 0.24 | 1613 | 2 | 0.1 | 0.07 | | | | |
| 75 to <85 | 1006 | 2 | 0.2 | 0.11 | 1085 | 1 | 0.1 | 0.05 | | | | |
| >=85 | 617 | 3 | 0.5 | 0.26 | 633 | 2 | 0.3 | 0.17 | | | | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.1.3: 1 Cox Regression for time to adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 251 | 4 | 1.6 | 0.97 | 263 | 1 | 0.4 | 0.22 | | | | |
| 30 to <45 | 899 | 6 | 0.7 | 0.37 | 909 | 2 | 0.2 | 0.12 | | | | |
| >=45 | 2128 | 2 | 0.1 | 0.05 | 2159 | 2 | 0.1 | 0.05 | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 1218 | 2 | 0.2 | 0.09 | 1243 | 2 | 0.2 | 0.09 | | | | |
| Microalbuminuria (30 to <=300) | 1549 | 5 | 0.3 | 0.18 | 1547 | 0 | 0 | 0.00 | | | | |
| Macroalbuminuria (>300) | 500 | 5 | 1.0 | 0.55 | 525 | 3 | 0.6 | 0.33 | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4810 |
| Low, moderate or high | 2432 | 3 | 0.1 | 0.07 | 2496 | 2 | 0.1 | 0.04 | 0.74 | (0.12, 4.42) | 0.7367 | |
| Very high | 836 | 9 | 1.1 | 0.61 | 820 | 3 | 0.4 | 0.21 | 0.33 | (0.09, 1.23) | 0.0983 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9920 |
| No | 573 | 4 | 0.7 | 0.37 | 579 | 0 | 0 | 0.00 | <0.01 | | 0.9917 | |
| Yes | 2706 | 8 | 0.3 | 0.16 | 2752 | 5 | 0.2 | 0.10 | 0.59 | (0.19, 1.82) | 0.3542 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5583 |
| No | 344 | 3 | 0.9 | 0.45 | 349 | 2 | 0.6 | 0.31 | 0.63 | (0.10, 3.81) | 0.6123 | |
| Yes | 2935 | 9 | 0.3 | 0.17 | 2982 | 3 | 0.1 | 0.06 | 0.32 | (0.09, 1.20) | 0.0913 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9939 |
| No | 275 | 1 | 0.4 | 0.18 | 307 | 0 | 0 | 0.00 | <0.01 | | 0.9936 | |
| Yes | 3004 | 11 | 0.4 | 0.20 | 3024 | 5 | 0.2 | 0.09 | 0.45 | (0.16, 1.30) | 0.1416 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.1.3: 2**

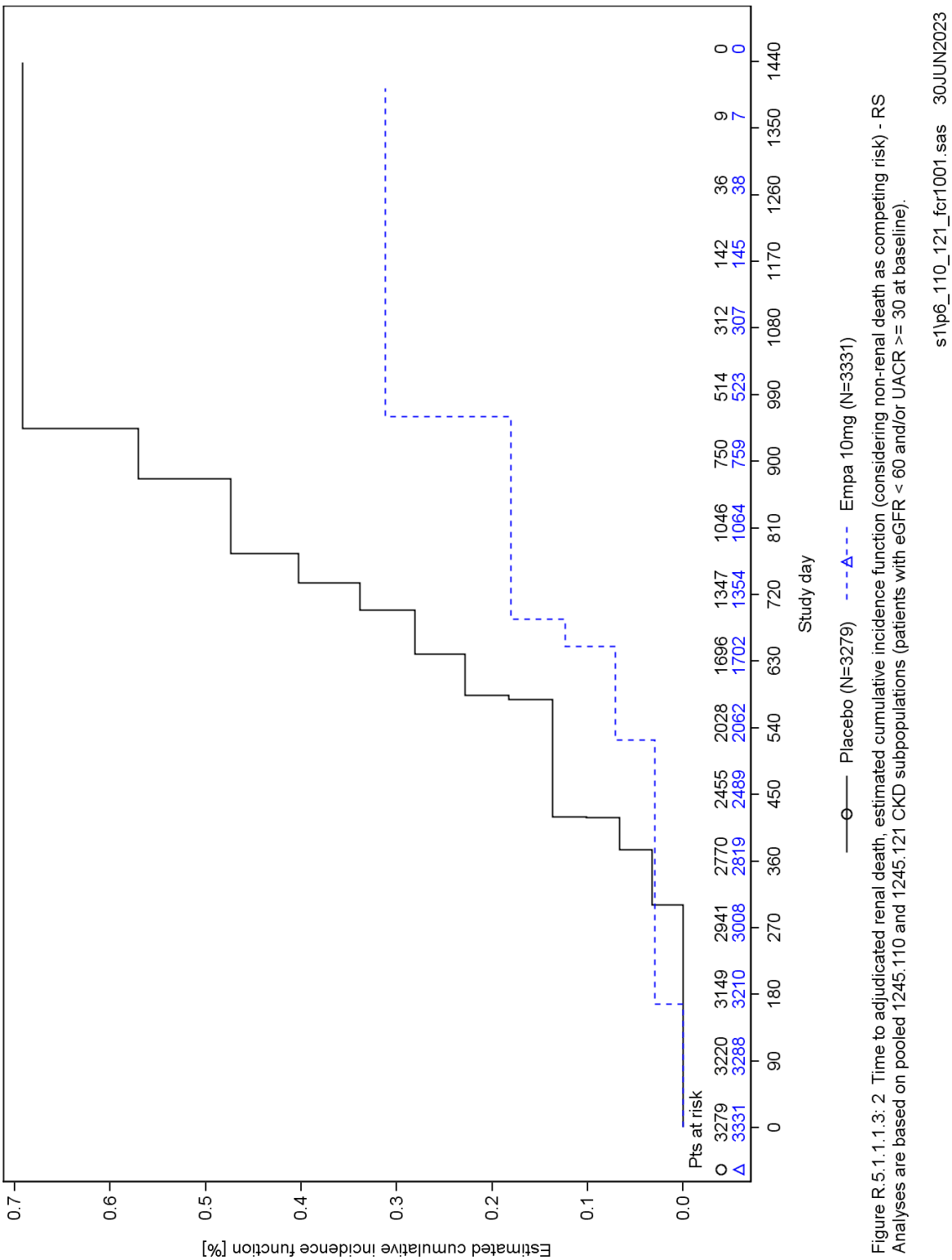


Figure R.5.1.1.1.3: 2 Time to adjudicated renal death, estimated cumulative incidence function (considering non-renal death as competing risk) - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.5.1.1.2**

R.5.1.1.2.1 Time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death

**Figure R.5.1.1.2.1: 1**

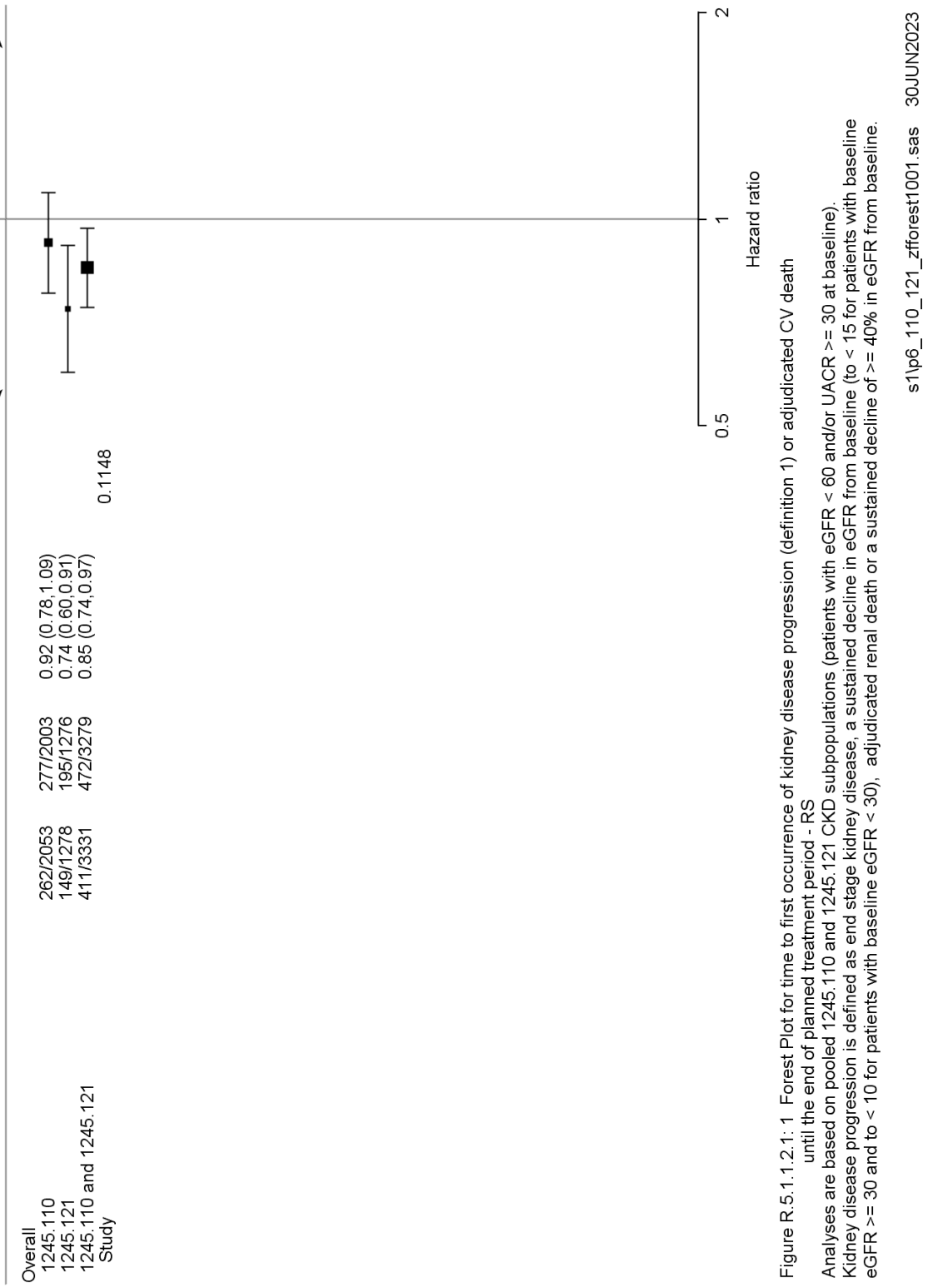


Figure R.5.1.1.2.1: 1 Forest Plot for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

Table R.5.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 472 | 14.4 | 10.11 | 3331 | 411 | 12.3 | 8.54 | 0.85 | (0.74,0.97) | 0.0144 | |
| Study | | | | | | | | | | | | 0.1148 |
| Sex | | | | | | | | | | | | 0.4261 |
| Male | 2024 | 298 | 14.7 | 10.62 | 2069 | 275 | 13.3 | 9.46 | 0.88 | (0.75,1.04) | 0.1333 | |
| Female | 1255 | 174 | 13.9 | 9.35 | 1262 | 136 | 10.8 | 7.13 | 0.79 | (0.63,0.99) | 0.0373 | |
| Age [years] | | | | | | | | | | | | 0.8836 |
| <65 | 767 | 115 | 15.0 | 11.46 | 705 | 91 | 12.9 | 9.77 | 0.86 | (0.66,1.14) | 0.2998 | |
| >=65 | 2512 | 357 | 14.2 | 9.74 | 2626 | 320 | 12.2 | 8.24 | 0.84 | (0.73,0.98) | 0.0281 | |
| Region | | | | | | | | | | | | 0.6754 |
| North America | 434 | 54 | 12.4 | 8.76 | 433 | 60 | 13.9 | 9.21 | 1.00 | (0.69,1.44) | 0.9996 | |
| Latin America | 931 | 159 | 17.1 | 13.56 | 944 | 139 | 14.7 | 11.53 | 0.86 | (0.68,1.08) | 0.1853 | |
| Europe | 1338 | 175 | 13.1 | 8.70 | 1361 | 136 | 10.0 | 6.57 | 0.76 | (0.61,0.95) | 0.0155 | |
| Asia | 405 | 53 | 13.1 | 8.52 | 413 | 46 | 11.1 | 7.16 | 0.85 | (0.57,1.26) | 0.4215 | |
| Other | 171 | 31 | 18.1 | 12.60 | 180 | 30 | 16.7 | 12.28 | 1.03 | (0.63,1.71) | 0.8994 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.4605 |
| Diabetic | 1742 | 275 | 15.8 | 11.29 | 1780 | 253 | 14.2 | 9.95 | 0.88 | (0.74,1.05) | 0.1533 | |
| Non-Diabetic | 1537 | 197 | 12.8 | 8.82 | 1551 | 158 | 10.2 | 6.96 | 0.80 | (0.65,0.98) | 0.0342 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1832 |
| <30 | 1977 | 307 | 15.5 | 11.27 | 1930 | 234 | 12.1 | 8.63 | 0.79 | (0.67,0.94) | 0.0072 | |
| >=30 | 1302 | 165 | 12.7 | 8.49 | 1401 | 177 | 12.6 | 8.42 | 0.95 | (0.77,1.18) | 0.6552 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.4424 |
| <130 | 1686 | 241 | 14.3 | 10.72 | 1687 | 194 | 11.5 | 8.46 | 0.80 | (0.66,0.97) | 0.0235 | |
| >=130 | 1593 | 231 | 14.5 | 9.55 | 1644 | 217 | 13.2 | 8.62 | 0.89 | (0.74,1.07) | 0.2244 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.9454 |
| <75 | 1656 | 252 | 15.2 | 10.97 | 1613 | 205 | 12.7 | 9.03 | 0.83 | (0.69,1.00) | 0.0536 | |
| 75 to <85 | 1006 | 142 | 14.1 | 9.52 | 1085 | 131 | 12.1 | 8.21 | 0.86 | (0.68,1.09) | 0.2047 | |
| >=85 | 617 | 78 | 12.6 | 8.87 | 633 | 75 | 11.8 | 7.92 | 0.89 | (0.65,1.22) | 0.4542 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

Table R.5.1.1.2.1: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.0729 |
| <30 | 251 | 63 | 25.1 | 20.13 | 263 | 47 | 17.9 | 13.22 | 0.62 | (0.42,0.90) | 0.0123 | |
| 30 to <45 | 899 | 120 | 13.3 | 9.34 | 909 | 121 | 13.3 | 9.31 | 1.03 | (0.80,1.33) | 0.8010 | |
| >=45 | 2128 | 289 | 13.6 | 9.41 | 2159 | 243 | 11.3 | 7.70 | 0.82 | (0.69,0.97) | 0.0196 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.2038 |
| Normal (<30) | 1218 | 124 | 10.2 | 7.03 | 1243 | 106 | 8.5 | 5.69 | 0.82 | (0.63,1.06) | 0.1268 | |
| Microalbuminuria (30 to <=300) | 1549 | 241 | 15.6 | 10.94 | 1547 | 188 | 12.2 | 8.51 | 0.79 | (0.65,0.95) | 0.0131 | |
| Macroalbuminuria (>300) | 500 | 105 | 21.0 | 15.19 | 525 | 116 | 22.1 | 16.09 | 1.05 | (0.81,1.37) | 0.7205 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3385 |
| Low, moderate or high | 2432 | 308 | 12.7 | 8.77 | 2496 | 262 | 10.5 | 7.16 | 0.82 | (0.69,0.96) | 0.0170 | |
| Very high | 836 | 162 | 19.4 | 14.10 | 820 | 149 | 18.2 | 13.12 | 0.94 | (0.75,1.17) | 0.5660 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9607 |
| No | 573 | 83 | 14.5 | 9.90 | 579 | 75 | 13.0 | 8.49 | 0.84 | (0.62,1.15) | 0.2795 | |
| Yes | 2706 | 389 | 14.4 | 10.16 | 2752 | 336 | 12.2 | 8.55 | 0.85 | (0.73,0.98) | 0.0280 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.1637 |
| No | 344 | 53 | 15.4 | 10.21 | 349 | 53 | 15.2 | 10.62 | 1.10 | (0.75,1.61) | 0.6360 | |
| Yes | 2935 | 419 | 14.3 | 10.10 | 2982 | 358 | 12.0 | 8.30 | 0.82 | (0.71,0.95) | 0.0063 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3575 |
| No | 275 | 35 | 12.7 | 7.76 | 307 | 24 | 7.8 | 4.98 | 0.67 | (0.40,1.13) | 0.1305 | |
| Yes | 3004 | 437 | 14.5 | 10.36 | 3024 | 387 | 12.8 | 8.94 | 0.86 | (0.75,0.99) | 0.0333 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

**Figure R.5.1.1.2.1: 2**

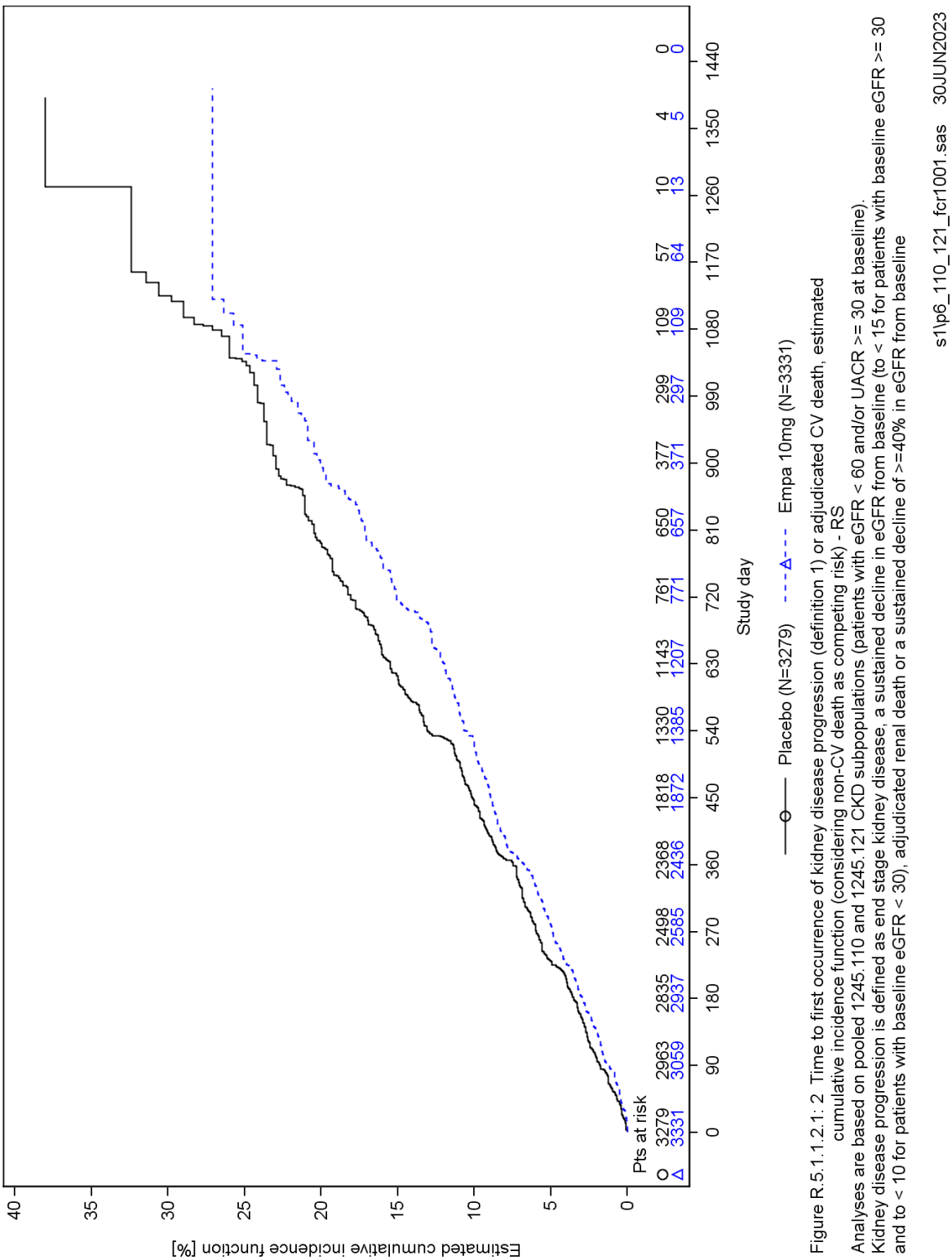


Figure R.5.1.1.2.1: 2 Time to first occurrence of kidney disease progression (definition 1) or adjudicated CV death, estimated cumulative incidence function (considering non-CV death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

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R.5.1.1.2.2 Time to first occurrence of kidney disease progression (definition 1)

**Figure R.5.1.1.2.2: 1**

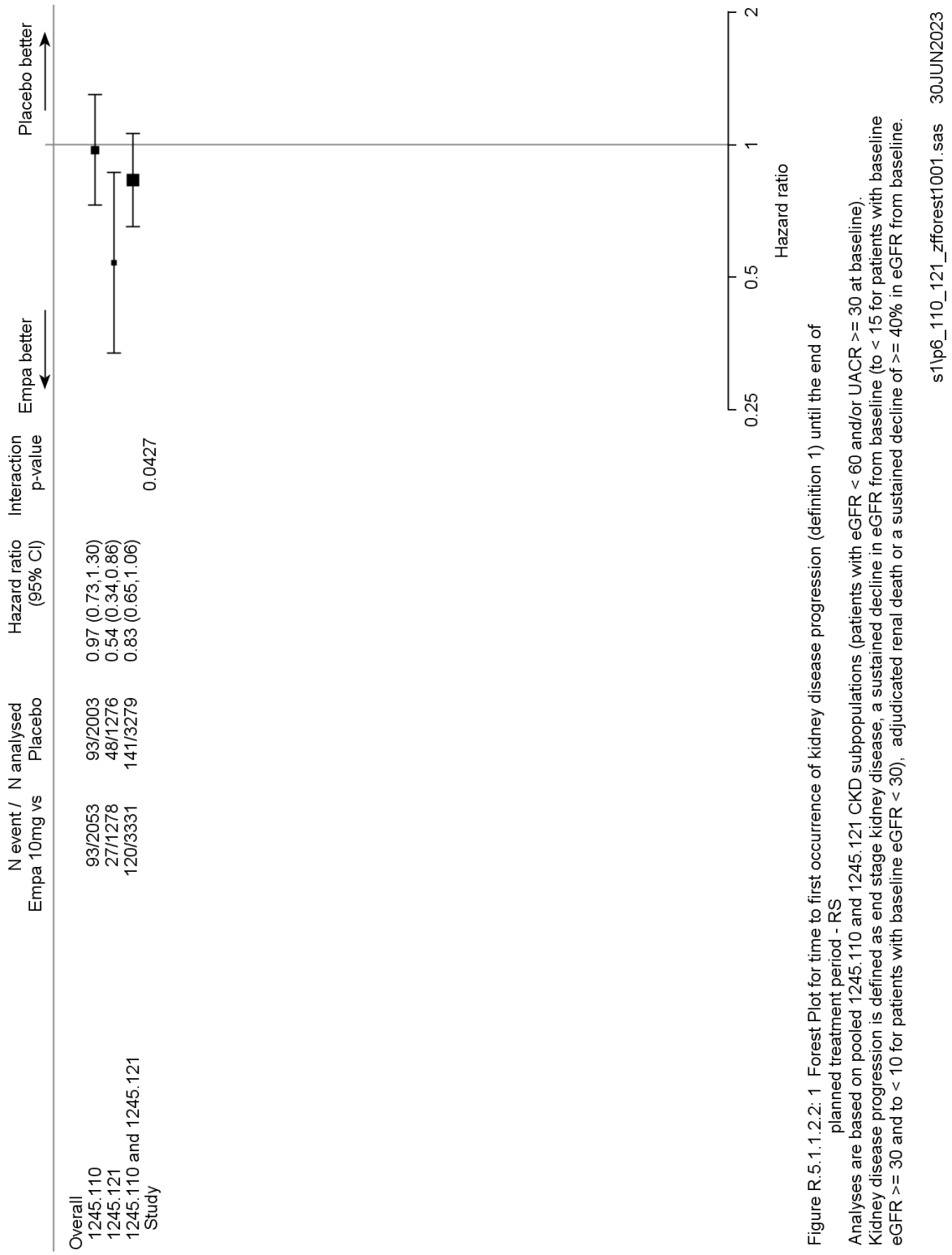


Figure R.5.1.1.2.2: 1 Forest Plot for time to first occurrence of kidney disease progression (definition 1) until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

Table R.5.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 141 | 4.3 | 3.09 | 3331 | 120 | 3.6 | 2.55 | 0.83 | (0.65,1.06) | 0.1335 | |
| Study | | | | | | | | | | | | 0.0427 |
| Sex | | | | | | | | | | | | 0.8642 |
| Male | 2024 | 82 | 4.1 | 2.99 | 2069 | 72 | 3.5 | 2.54 | 0.84 | (0.62,1.16) | 0.2962 | |
| Female | 1255 | 59 | 4.7 | 3.23 | 1262 | 48 | 3.8 | 2.56 | 0.81 | (0.55,1.18) | 0.2756 | |
| Age [years] | | | | | | | | | | | | 0.7797 |
| <65 | 767 | 47 | 6.1 | 4.78 | 705 | 35 | 5.0 | 3.82 | 0.79 | (0.51,1.23) | 0.3034 | |
| >=65 | 2512 | 94 | 3.7 | 2.62 | 2626 | 85 | 3.2 | 2.24 | 0.86 | (0.64,1.15) | 0.3013 | |
| Region | | | | | | | | | | | | 0.4996 |
| North America | 434 | 17 | 3.9 | 2.82 | 433 | 19 | 4.4 | 3.00 | 1.07 | (0.56,2.06) | 0.8400 | |
| Latin America | 931 | 50 | 5.4 | 4.36 | 944 | 42 | 4.4 | 3.58 | 0.82 | (0.54,1.24) | 0.3440 | |
| Europe | 1338 | 42 | 3.1 | 2.14 | 1361 | 26 | 1.9 | 1.28 | 0.59 | (0.36,0.96) | 0.0340 | |
| Asia | 405 | 18 | 4.4 | 2.93 | 413 | 19 | 4.6 | 2.99 | 0.99 | (0.52,1.88) | 0.9640 | |
| Other | 171 | 14 | 8.2 | 5.78 | 180 | 14 | 7.8 | 5.88 | 1.12 | (0.53,2.35) | 0.7678 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3419 |
| Diabetic | 1742 | 96 | 5.5 | 4.03 | 1780 | 89 | 5.0 | 3.58 | 0.90 | (0.67,1.20) | 0.4585 | |
| Non-Diabetic | 1537 | 45 | 2.9 | 2.06 | 1551 | 31 | 2.0 | 1.39 | 0.69 | (0.44,1.09) | 0.1116 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5088 |
| <30 | 1977 | 78 | 3.9 | 2.93 | 1930 | 57 | 3.0 | 2.15 | 0.76 | (0.54,1.07) | 0.1190 | |
| >=30 | 1302 | 63 | 4.8 | 3.31 | 1401 | 63 | 4.5 | 3.06 | 0.90 | (0.63,1.27) | 0.5484 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1566 |
| <130 | 1686 | 63 | 3.7 | 2.86 | 1687 | 40 | 2.4 | 1.79 | 0.66 | (0.44,0.98) | 0.0378 | |
| >=130 | 1593 | 78 | 4.9 | 3.30 | 1644 | 80 | 4.9 | 3.24 | 0.95 | (0.69,1.29) | 0.7298 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2140 |
| <75 | 1656 | 72 | 4.3 | 3.21 | 1613 | 46 | 2.9 | 2.07 | 0.65 | (0.45,0.94) | 0.0237 | |
| 75 to <85 | 1006 | 38 | 3.8 | 2.61 | 1085 | 44 | 4.1 | 2.82 | 1.07 | (0.69,1.65) | 0.7650 | |
| >=85 | 617 | 31 | 5.0 | 3.59 | 633 | 30 | 4.7 | 3.23 | 0.92 | (0.56,1.52) | 0.7447 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

Table R.5.1.1.2.2: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 1) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.3119 |
| <30 | 251 | 25 | 10.0 | 8.32 | 263 | 17 | 6.5 | 4.95 | 0.53 | (0.28,0.98) | 0.0419 | |
| 30 to <45 | 899 | 39 | 4.3 | 3.10 | 909 | 33 | 3.6 | 2.60 | 0.86 | (0.54,1.37) | 0.5254 | |
| >=45 | 2128 | 77 | 3.6 | 2.56 | 2159 | 70 | 3.2 | 2.26 | 0.90 | (0.65,1.24) | 0.5224 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9740 |
| Normal (<30) | 1218 | 30 | 2.5 | 1.73 | 1243 | 24 | 1.9 | 1.31 | 0.78 | (0.45,1.33) | 0.3560 | |
| Microalbuminuria (30 to <=300) | 1549 | 61 | 3.9 | 2.83 | 1547 | 50 | 3.2 | 2.32 | 0.83 | (0.57,1.21) | 0.3375 | |
| Macroalbuminuria (>300) | 500 | 50 | 10.0 | 7.44 | 525 | 46 | 8.8 | 6.60 | 0.83 | (0.56,1.25) | 0.3763 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7466 |
| Low, moderate or high | 2432 | 80 | 3.3 | 2.32 | 2496 | 71 | 2.8 | 1.98 | 0.87 | (0.63,1.19) | 0.3800 | |
| Very high | 836 | 61 | 7.3 | 5.47 | 820 | 49 | 6.0 | 4.45 | 0.80 | (0.55,1.16) | 0.2425 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6036 |
| No | 573 | 21 | 3.7 | 2.56 | 579 | 22 | 3.8 | 2.55 | 0.96 | (0.53,1.75) | 0.8961 | |
| Yes | 2706 | 120 | 4.4 | 3.20 | 2752 | 98 | 3.6 | 2.55 | 0.81 | (0.62,1.06) | 0.1173 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.1963 |
| No | 344 | 16 | 4.7 | 3.14 | 349 | 18 | 5.2 | 3.70 | 1.26 | (0.64,2.48) | 0.4997 | |
| Yes | 2935 | 125 | 4.3 | 3.08 | 2982 | 102 | 3.4 | 2.42 | 0.78 | (0.60,1.02) | 0.0669 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.6254 |
| No | 275 | 8 | 2.9 | 1.81 | 307 | 5 | 1.6 | 1.05 | 0.63 | (0.21,1.93) | 0.4202 | |
| Yes | 3004 | 133 | 4.4 | 3.23 | 3024 | 115 | 3.8 | 2.72 | 0.84 | (0.65,1.08) | 0.1715 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 40% in eGFR from baseline.

**Figure R.5.1.1.2.2: 2**

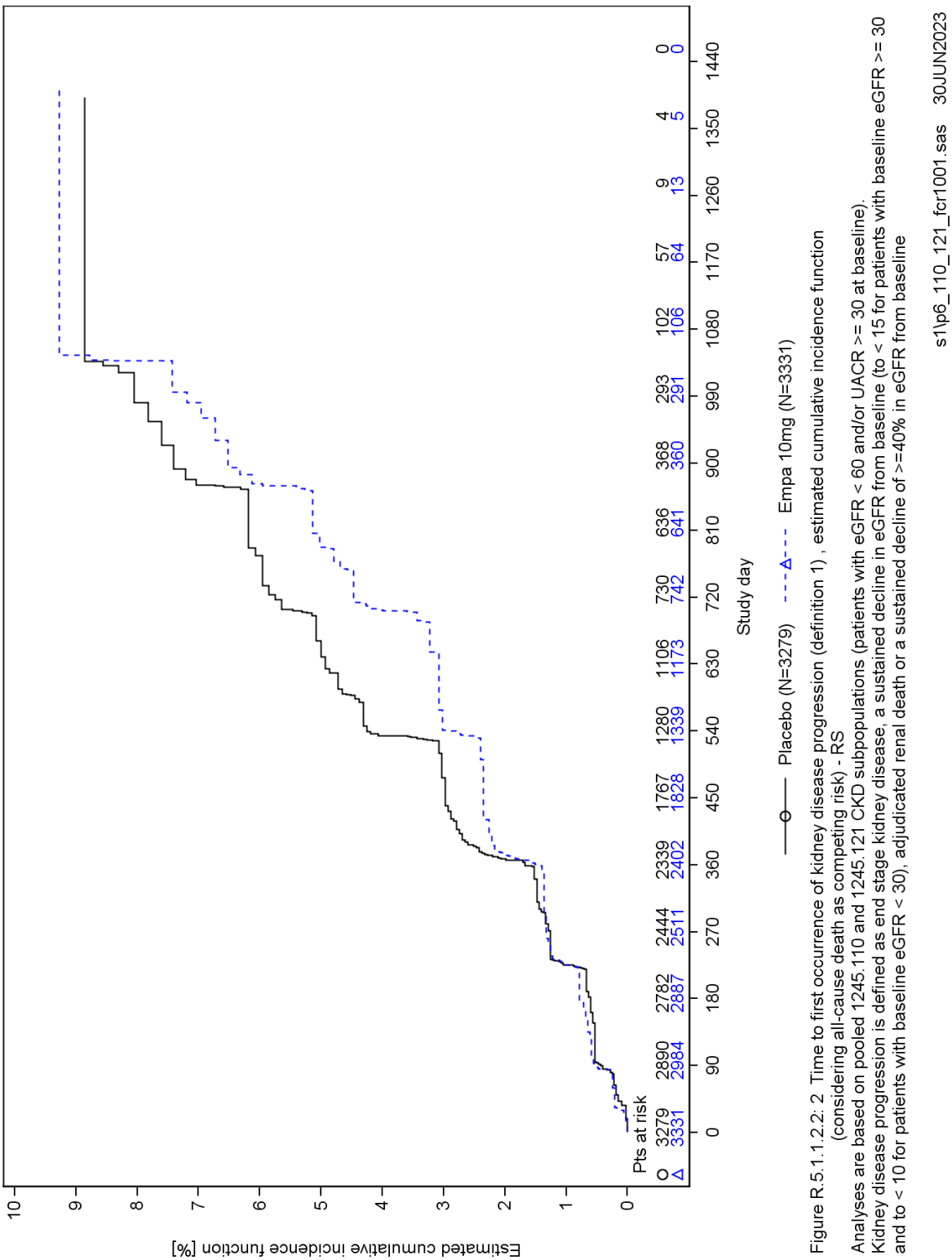


Figure R.5.1.1.2.2: 2 Time to first occurrence of kidney disease progression (definition 1) , estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=40% in eGFR from baseline

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R.5.1.1.2.3 Time to first occurrence of kidney disease progression (definition 2)

**Figure R.5.1.1.2.3: 1**

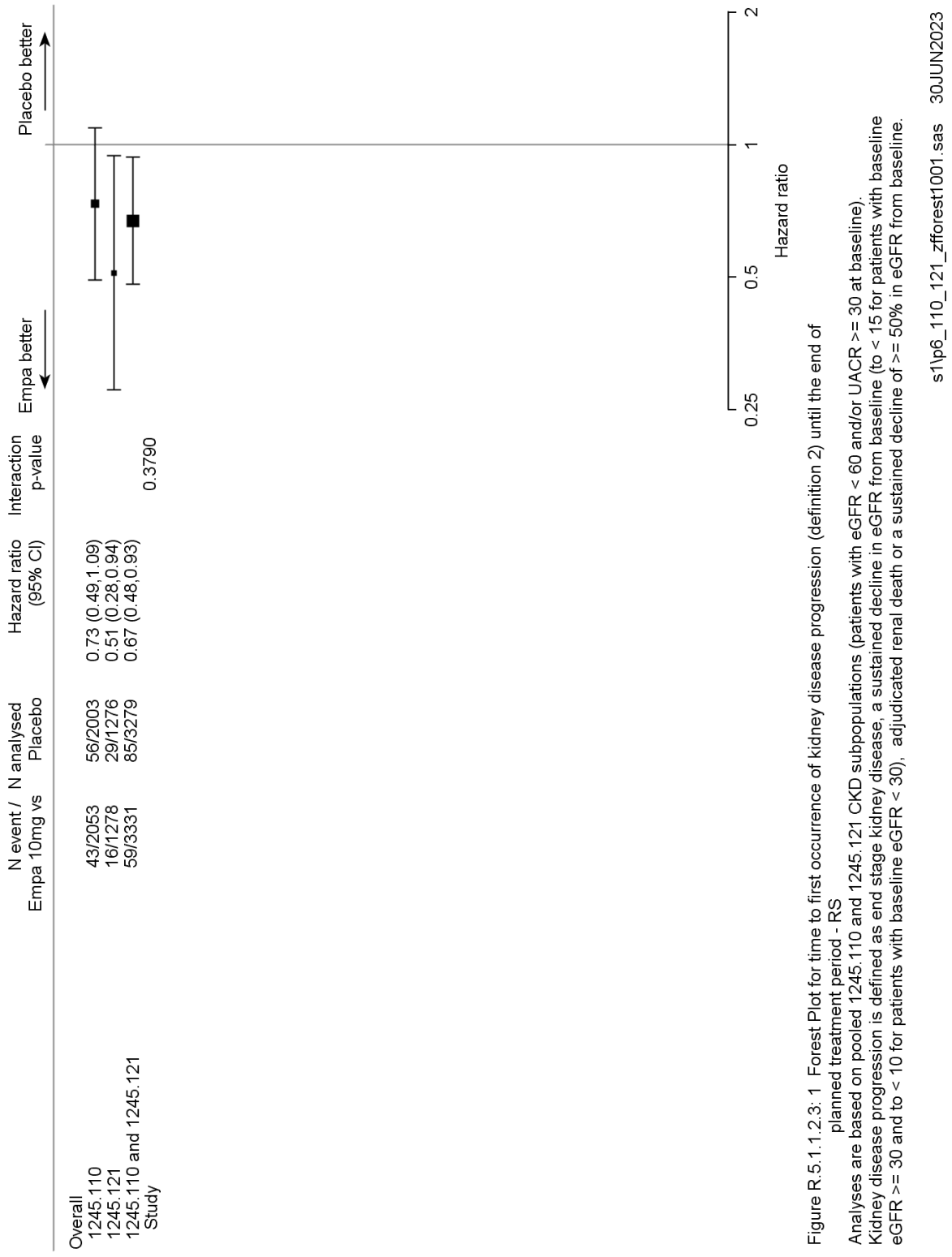


Figure R.5.1.1.2.3: 1 Forest Plot for time to first occurrence of kidney disease progression (definition 2) until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 50% in eGFR from baseline.

Table R.5.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 85 | 2.6 | 1.84 | 3331 | 59 | 1.8 | 1.24 | 0.67 | (0.48,0.93) | 0.0183 | |
| Study | | | | | | | | | | | | 0.3790 |
| Sex | | | | | | | | | | | | 0.4175 |
| Male | 2024 | 54 | 2.7 | 1.96 | 2069 | 42 | 2.0 | 1.47 | 0.74 | (0.49,1.10) | 0.1393 | |
| Female | 1255 | 31 | 2.5 | 1.68 | 1262 | 17 | 1.3 | 0.90 | 0.55 | (0.30,0.99) | 0.0467 | |
| Age [years] | | | | | | | | | | | | 0.6184 |
| <65 | 767 | 33 | 4.3 | 3.32 | 705 | 19 | 2.7 | 2.04 | 0.60 | (0.34,1.06) | 0.0787 | |
| >=65 | 2512 | 52 | 2.1 | 1.44 | 2626 | 40 | 1.5 | 1.05 | 0.72 | (0.48,1.09) | 0.1176 | |
| Region | | | | | | | | | | | | 0.7406 |
| North America | 434 | 15 | 3.5 | 2.47 | 433 | 14 | 3.2 | 2.19 | 0.89 | (0.43,1.84) | 0.7472 | |
| Latin America | 931 | 30 | 3.2 | 2.58 | 944 | 21 | 2.2 | 1.77 | 0.68 | (0.39,1.19) | 0.1798 | |
| Europe | 1338 | 23 | 1.7 | 1.17 | 1361 | 11 | 0.8 | 0.54 | 0.45 | (0.22,0.91) | 0.0275 | |
| Asia | 405 | 9 | 2.2 | 1.45 | 413 | 8 | 1.9 | 1.24 | 0.81 | (0.31,2.10) | 0.6641 | |
| Other | 171 | 8 | 4.7 | 3.27 | 180 | 5 | 2.8 | 2.04 | 0.71 | (0.23,2.18) | 0.5538 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2296 |
| Diabetic | 1742 | 61 | 3.5 | 2.54 | 1780 | 48 | 2.7 | 1.91 | 0.75 | (0.51,1.10) | 0.1397 | |
| Non-Diabetic | 1537 | 24 | 1.6 | 1.09 | 1551 | 11 | 0.7 | 0.49 | 0.46 | (0.22,0.94) | 0.0320 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9798 |
| <30 | 1977 | 47 | 2.4 | 1.75 | 1930 | 30 | 1.6 | 1.13 | 0.67 | (0.43,1.07) | 0.0918 | |
| >=30 | 1302 | 38 | 2.9 | 1.98 | 1401 | 29 | 2.1 | 1.39 | 0.67 | (0.41,1.08) | 0.1027 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.1617 |
| <130 | 1686 | 40 | 2.4 | 1.80 | 1687 | 19 | 1.1 | 0.84 | 0.49 | (0.28,0.85) | 0.0106 | |
| >=130 | 1593 | 45 | 2.8 | 1.88 | 1644 | 40 | 2.4 | 1.60 | 0.80 | (0.52,1.23) | 0.3189 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.9700 |
| <75 | 1656 | 44 | 2.7 | 1.94 | 1613 | 29 | 1.8 | 1.30 | 0.67 | (0.42,1.08) | 0.0991 | |
| 75 to <85 | 1006 | 22 | 2.2 | 1.50 | 1085 | 17 | 1.6 | 1.08 | 0.71 | (0.37,1.33) | 0.2826 | |
| >=85 | 617 | 19 | 3.1 | 2.18 | 633 | 13 | 2.1 | 1.38 | 0.63 | (0.31,1.27) | 0.1967 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 50% in eGFR from baseline.

Table R.5.1.1.2.3: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 2) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.7445 |
| <30 | 251 | 17 | 6.8 | 5.59 | 263 | 12 | 4.6 | 3.47 | 0.51 | (0.24,1.06) | 0.0724 | |
| 30 to <45 | 899 | 24 | 2.7 | 1.88 | 909 | 17 | 1.9 | 1.32 | 0.72 | (0.39,1.35) | 0.3104 | |
| >=45 | 2128 | 44 | 2.1 | 1.45 | 2159 | 30 | 1.4 | 0.96 | 0.68 | (0.43,1.08) | 0.1055 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.3108 |
| Normal (<30) | 1218 | 17 | 1.4 | 0.97 | 1243 | 6 | 0.5 | 0.32 | 0.34 | (0.13,0.87) | 0.0240 | |
| Microalbuminuria (30 to <=300) | 1549 | 36 | 2.3 | 1.66 | 1547 | 25 | 1.6 | 1.15 | 0.70 | (0.42,1.17) | 0.1731 | |
| Macroalbuminuria (>300) | 500 | 32 | 6.4 | 4.69 | 525 | 28 | 5.3 | 3.93 | 0.77 | (0.46,1.29) | 0.3264 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4159 |
| Low, moderate or high | 2432 | 44 | 1.8 | 1.27 | 2496 | 26 | 1.0 | 0.72 | 0.59 | (0.36,0.95) | 0.0305 | |
| Very high | 836 | 41 | 4.9 | 3.63 | 820 | 33 | 4.0 | 2.97 | 0.77 | (0.49,1.22) | 0.2713 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7480 |
| No | 573 | 16 | 2.8 | 1.94 | 579 | 13 | 2.2 | 1.50 | 0.75 | (0.36,1.55) | 0.4311 | |
| Yes | 2706 | 69 | 2.5 | 1.82 | 2752 | 46 | 1.7 | 1.18 | 0.65 | (0.45,0.95) | 0.0244 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3127 |
| No | 344 | 11 | 3.2 | 2.14 | 349 | 10 | 2.9 | 2.03 | 1.02 | (0.43,2.40) | 0.9706 | |
| Yes | 2935 | 74 | 2.5 | 1.81 | 2982 | 49 | 1.6 | 1.15 | 0.63 | (0.44,0.90) | 0.0120 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.1388 |
| No | 275 | 7 | 2.5 | 1.57 | 307 | 1 | 0.3 | 0.21 | 0.14 | (0.02,1.17) | 0.0698 | |
| Yes | 3004 | 78 | 2.6 | 1.87 | 3024 | 58 | 1.9 | 1.36 | 0.71 | (0.51,1.01) | 0.0535 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 50% in eGFR from baseline.

**Figure R.5.1.1.2.3: 2**

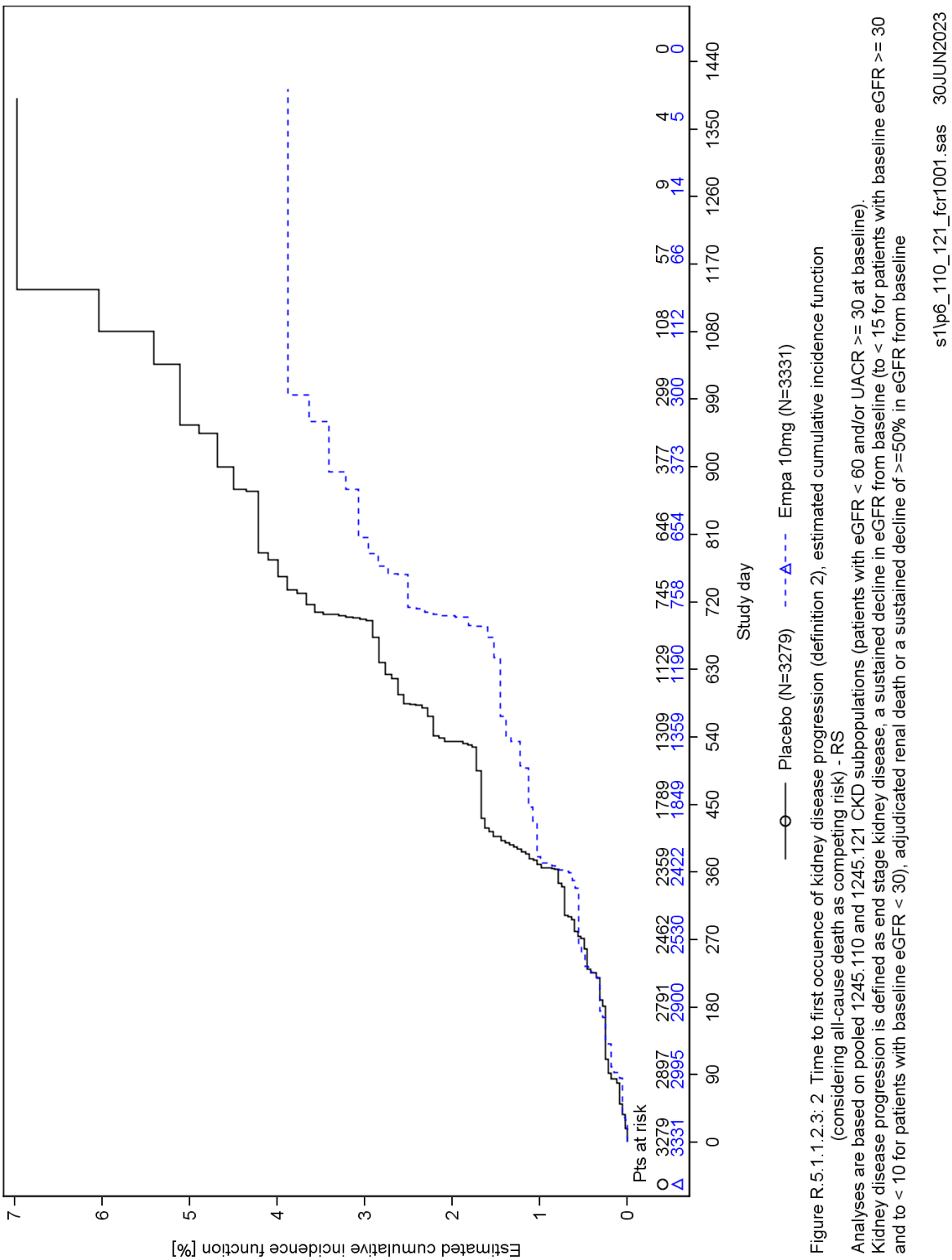


Figure R.5.1.1.2.3: 2 Time to first occuence of kidney disease progression (definition 2), estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=50% in eGFR from baseline

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R.5.1.1.2.4 Time to first occurrence of kidney disease progression (definition 3)

**Figure R.5.1.1.2.4: 1**

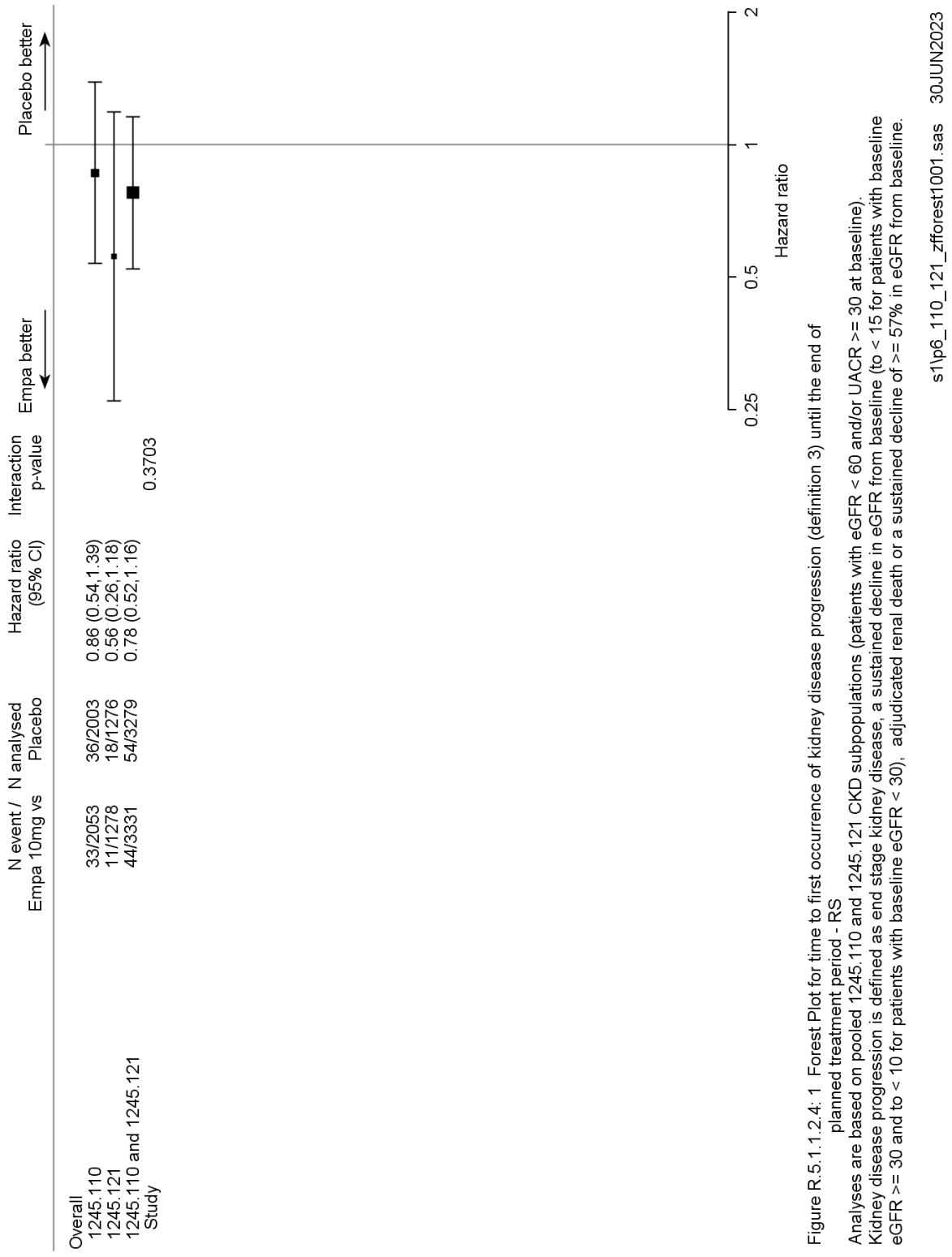


Figure R.5.1.1.2.4: 1 Forest Plot for time to first occurrence of kidney disease progression (definition 3) until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 57% in eGFR from baseline.

Table R.5.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 54 | 1.6 | 1.17 | 3331 | 44 | 1.3 | 0.92 | 0.78 | (0.52,1.16) | 0.2137 | |
| Study | | | | | | | | | | | | 0.3703 |
| Sex | | | | | | | | | | | | 0.6689 |
| Male | 2024 | 35 | 1.7 | 1.27 | 2069 | 31 | 1.5 | 1.08 | 0.82 | (0.51,1.34) | 0.4346 | |
| Female | 1255 | 19 | 1.5 | 1.02 | 1262 | 13 | 1.0 | 0.69 | 0.68 | (0.34,1.39) | 0.2920 | |
| Age [years] | | | | | | | | | | | | 0.6588 |
| <65 | 767 | 22 | 2.9 | 2.21 | 705 | 15 | 2.1 | 1.61 | 0.70 | (0.36,1.35) | 0.2889 | |
| >=65 | 2512 | 32 | 1.3 | 0.88 | 2626 | 29 | 1.1 | 0.76 | 0.84 | (0.51,1.40) | 0.5095 | |
| Region | | | | | | | | | | | | 0.9373 |
| North America | 434 | 11 | 2.5 | 1.80 | 433 | 11 | 2.5 | 1.72 | 0.95 | (0.41,2.19) | 0.9018 | |
| Latin America | 931 | 20 | 2.1 | 1.72 | 944 | 17 | 1.8 | 1.43 | 0.82 | (0.43,1.56) | 0.5375 | |
| Europe | 1338 | 13 | 1.0 | 0.66 | 1361 | 8 | 0.6 | 0.39 | 0.57 | (0.23,1.37) | 0.2070 | |
| Asia | 405 | 5 | 1.2 | 0.80 | 413 | 5 | 1.2 | 0.77 | 0.88 | (0.26,3.05) | 0.8432 | |
| Other | 171 | 5 | 2.9 | 2.03 | 180 | 3 | 1.7 | 1.22 | 0.68 | (0.16,2.83) | 0.5909 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.2045 |
| Diabetic | 1742 | 39 | 2.2 | 1.62 | 1780 | 37 | 2.1 | 1.47 | 0.90 | (0.57,1.41) | 0.6327 | |
| Non-Diabetic | 1537 | 15 | 1.0 | 0.68 | 1551 | 7 | 0.5 | 0.31 | 0.47 | (0.19,1.15) | 0.0968 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9568 |
| <30 | 1977 | 30 | 1.5 | 1.11 | 1930 | 22 | 1.1 | 0.82 | 0.77 | (0.44,1.34) | 0.3568 | |
| >=30 | 1302 | 24 | 1.8 | 1.24 | 1401 | 22 | 1.6 | 1.05 | 0.79 | (0.44,1.41) | 0.4230 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0121 |
| <130 | 1686 | 29 | 1.7 | 1.31 | 1687 | 11 | 0.7 | 0.49 | 0.39 | (0.19,0.78) | 0.0075 | |
| >=130 | 1593 | 25 | 1.6 | 1.04 | 1644 | 33 | 2.0 | 1.32 | 1.18 | (0.70,1.99) | 0.5331 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4812 |
| <75 | 1656 | 25 | 1.5 | 1.10 | 1613 | 21 | 1.3 | 0.94 | 0.86 | (0.48,1.53) | 0.6031 | |
| 75 to <85 | 1006 | 20 | 2.0 | 1.36 | 1085 | 12 | 1.1 | 0.76 | 0.55 | (0.27,1.12) | 0.1005 | |
| >=85 | 617 | 9 | 1.5 | 1.02 | 633 | 11 | 1.7 | 1.17 | 1.05 | (0.43,2.56) | 0.9084 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 57% in eGFR from baseline.

Table R.5.1.1.2.4: 1 Cox Regression for time to first occurrence of kidney disease progression (definition 3) until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.5658 |
| <30 | 251 | 13 | 5.2 | 4.28 | 263 | 12 | 4.6 | 3.47 | 0.66 | (0.30,1.46) | 0.3083 | |
| 30 to <45 | 899 | 19 | 2.1 | 1.49 | 909 | 11 | 1.2 | 0.86 | 0.59 | (0.28,1.23) | 0.1604 | |
| >=45 | 2128 | 22 | 1.0 | 0.72 | 2159 | 21 | 1.0 | 0.67 | 0.96 | (0.53,1.74) | 0.8833 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4294 |
| Normal (<30) | 1218 | 12 | 1.0 | 0.69 | 1243 | 5 | 0.4 | 0.27 | 0.41 | (0.14,1.16) | 0.0929 | |
| Microalbuminuria (30 to <=300) | 1549 | 20 | 1.3 | 0.92 | 1547 | 18 | 1.2 | 0.83 | 0.90 | (0.47,1.70) | 0.7350 | |
| Macroalbuminuria (>300) | 500 | 22 | 4.4 | 3.21 | 525 | 21 | 4.0 | 2.94 | 0.83 | (0.45,1.52) | 0.5445 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.8087 |
| Low, moderate or high | 2432 | 24 | 1.0 | 0.69 | 2496 | 18 | 0.7 | 0.50 | 0.74 | (0.40,1.37) | 0.3442 | |
| Very high | 836 | 30 | 3.6 | 2.65 | 820 | 26 | 3.2 | 2.33 | 0.82 | (0.49,1.39) | 0.4669 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.4812 |
| No | 573 | 11 | 1.9 | 1.33 | 579 | 7 | 1.2 | 0.80 | 0.57 | (0.22,1.47) | 0.2472 | |
| Yes | 2706 | 43 | 1.6 | 1.13 | 2752 | 37 | 1.3 | 0.95 | 0.83 | (0.54,1.29) | 0.4126 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.1877 |
| No | 344 | 6 | 1.7 | 1.16 | 349 | 8 | 2.3 | 1.62 | 1.51 | (0.52,4.37) | 0.4427 | |
| Yes | 2935 | 48 | 1.6 | 1.17 | 2982 | 36 | 1.2 | 0.84 | 0.70 | (0.45,1.08) | 0.1087 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9778 |
| No | 275 | 3 | 1.1 | 0.67 | 307 | 0 | 0 | 0.00 | <0.01 | | 0.9775 | |
| Yes | 3004 | 51 | 1.7 | 1.22 | 3024 | 44 | 1.5 | 1.03 | 0.82 | (0.55,1.23) | 0.3354 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >= 57% in eGFR from baseline.

**Figure R.5.1.1.2.4: 2**

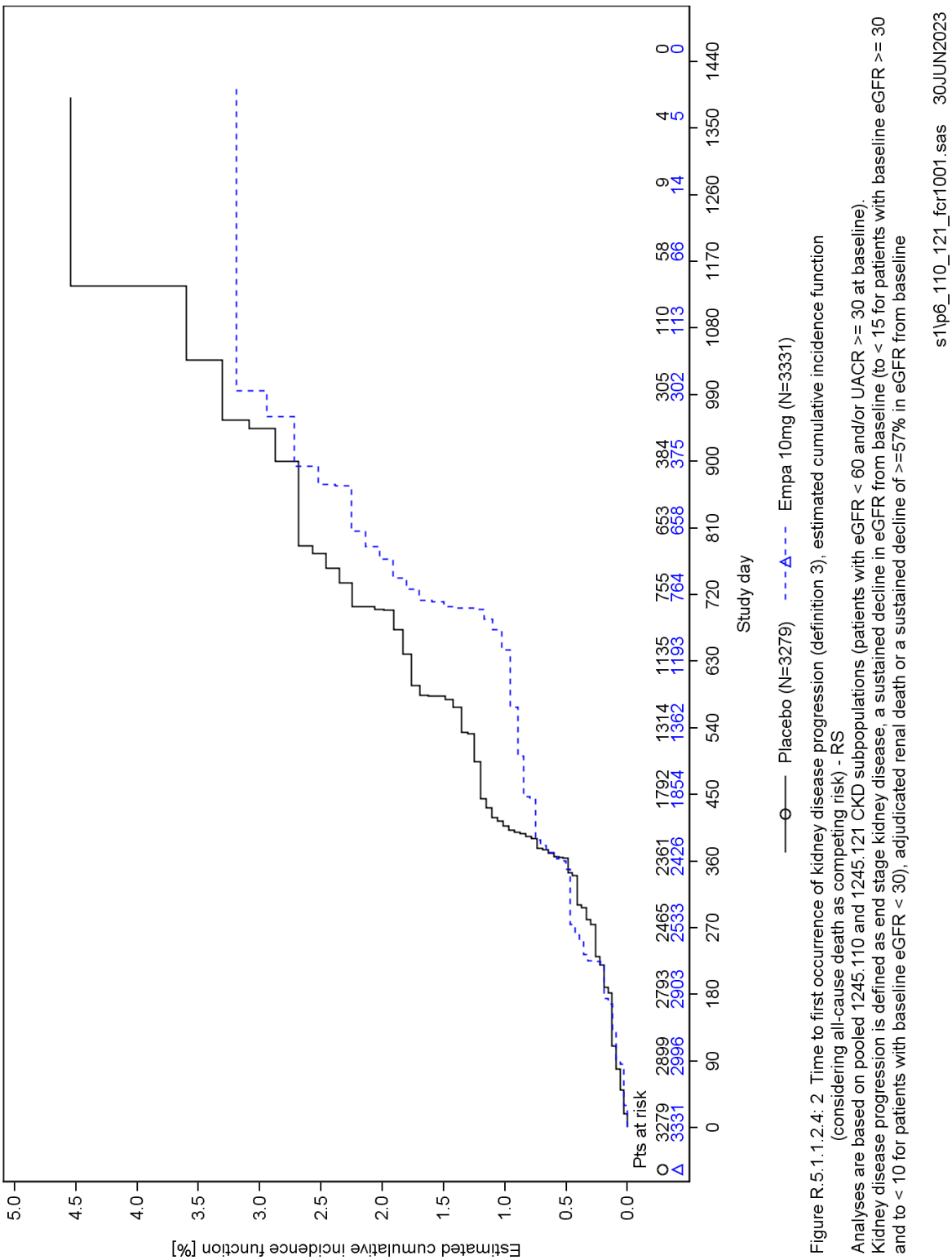


Figure R.5.1.1.2.4: 2 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=57% in eGFR from baseline

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**Figure R.5.1.1.2.4: 3**

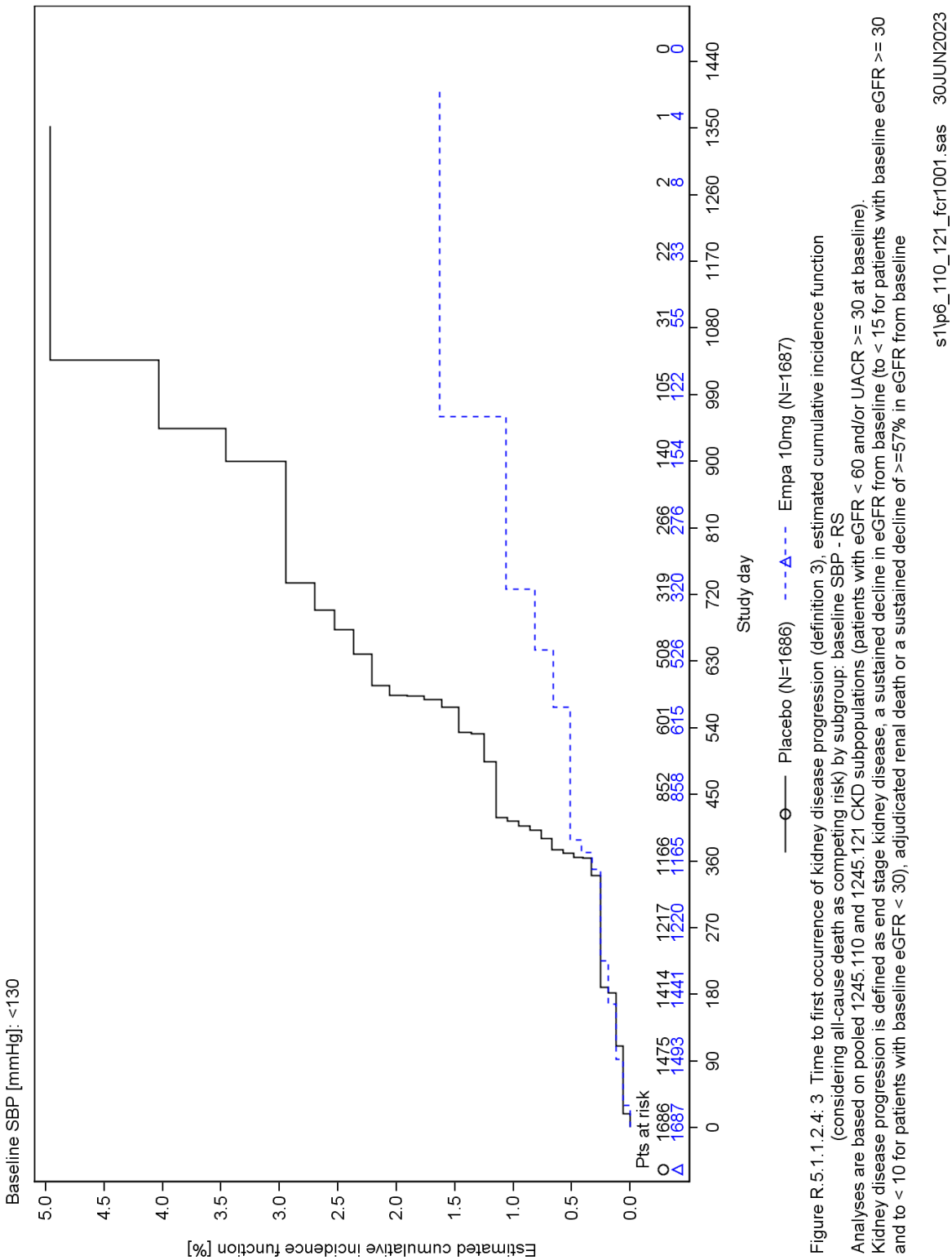


Figure R.5.1.1.2.4: 3 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=57% in eGFR from baseline

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**Figure R.5.1.1.2.4: 3**

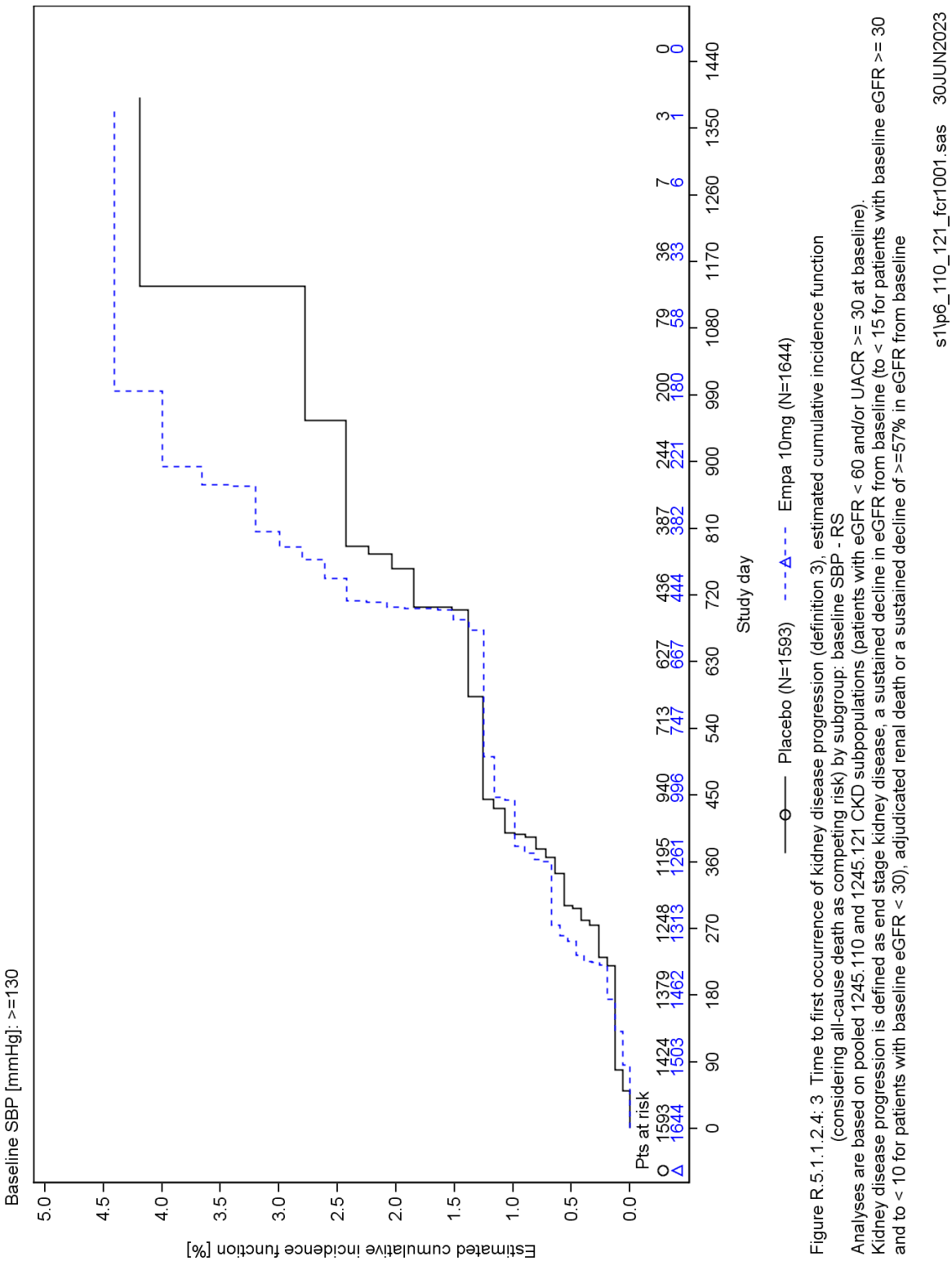


Figure R.5.1.1.2.4: 3 Time to first occurrence of kidney disease progression (definition 3), estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Kidney disease progression is defined as end stage kidney disease, a sustained decline in eGFR from baseline (to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30), adjudicated renal death or a sustained decline of >=57% in eGFR from baseline

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R.5.1.1.2.5

R.5.1.1.2.5 Time to first occurrence of sustained decline of >= 40% in eGFR

**Figure R.5.1.1.2.5: 1**

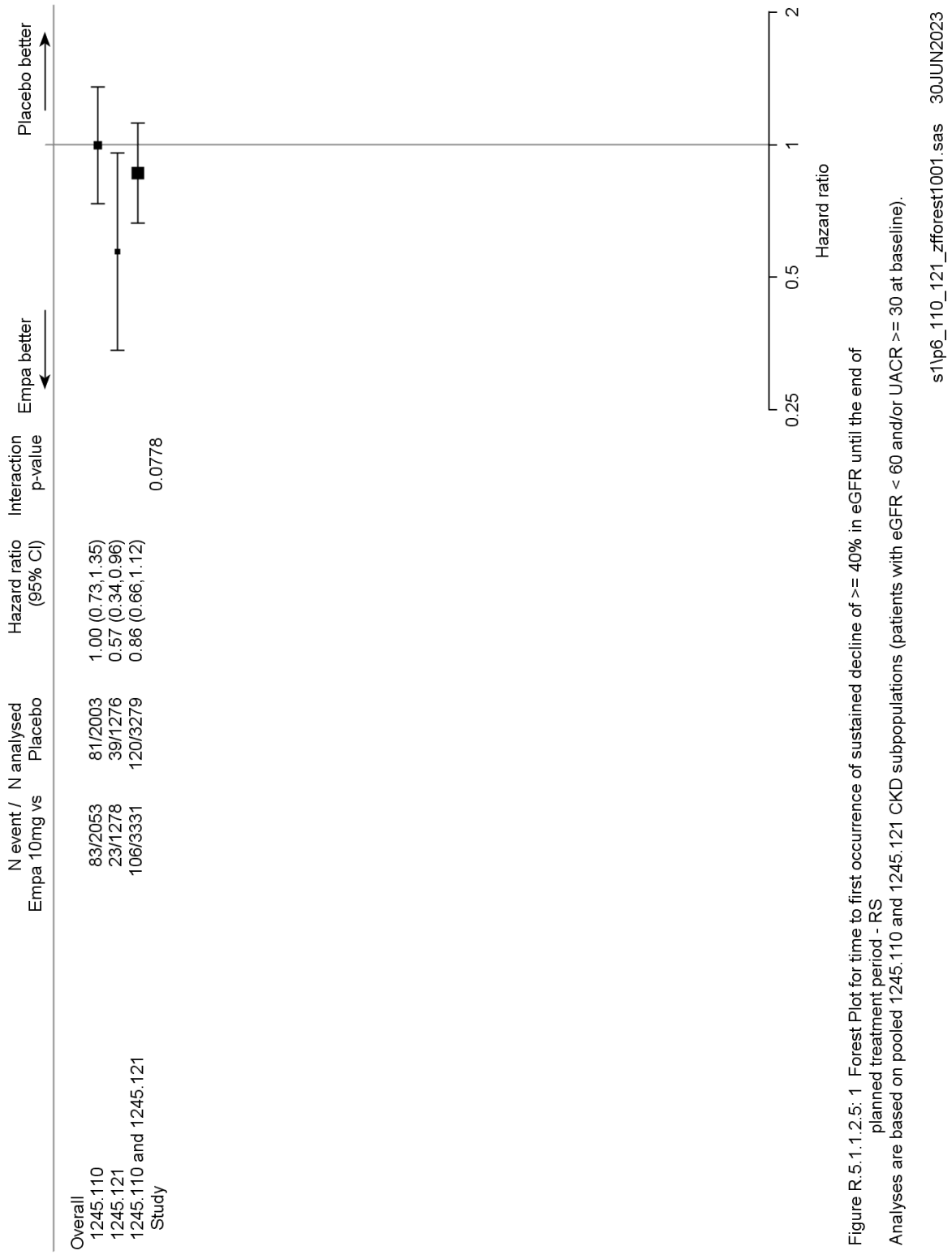


Figure R.5.1.1.2.5: 1 Forest Plot for time to first occurrence of sustained decline of >= 40% in eGFR until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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Table R.5.1.1.2.5: 1 Cox Regression for time to first occurrence of sustained decline of >= 40% in eGFR until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3279 | 120 | 3.7 | 2.63 | 3331 | 106 | 3.2 | 2.25 | 0.86 | (0.66,1.12) | 0.2638 | |
| Study | | | | | | | | | | | | 0.0778 |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, subgroup, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.2.5: 2**

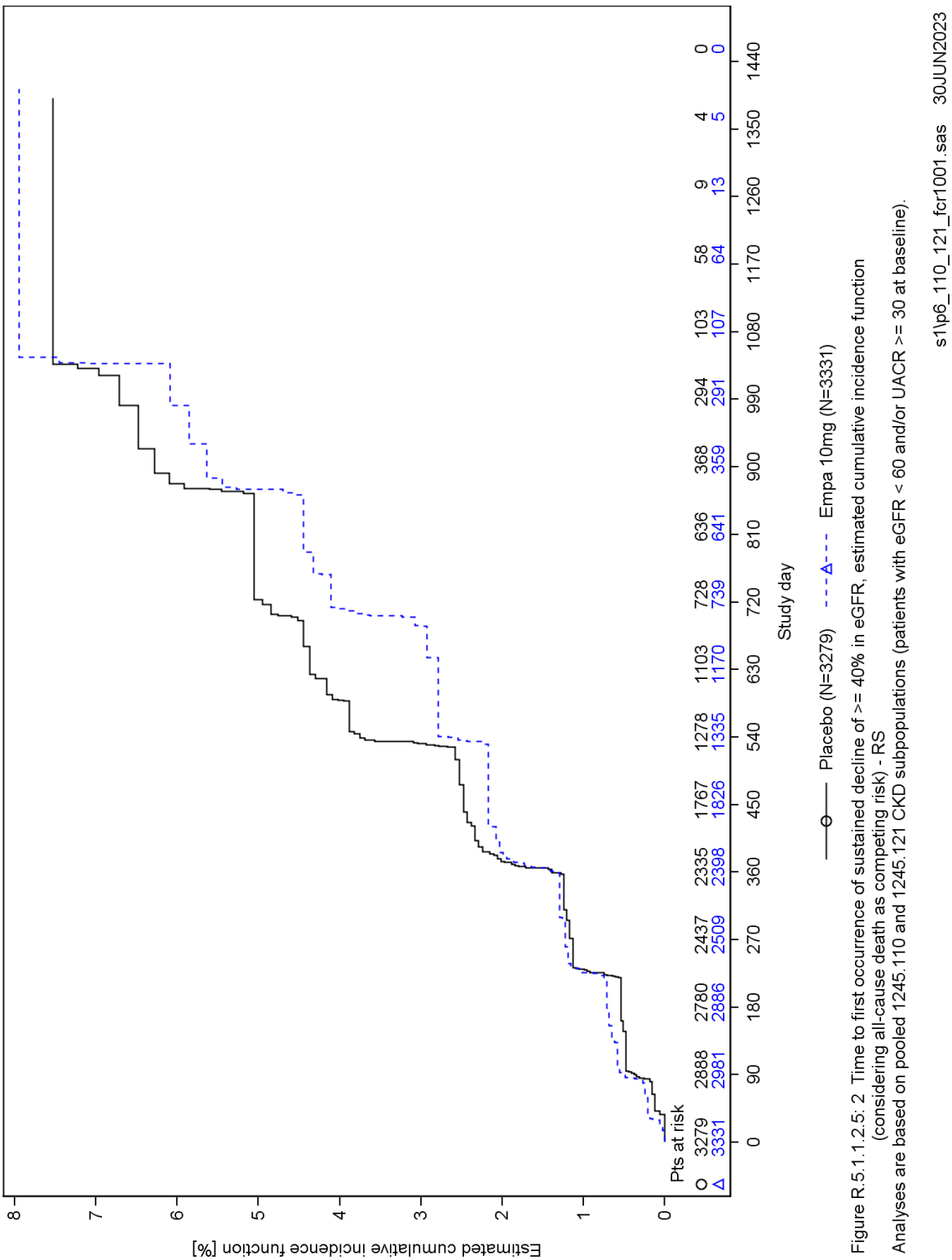


Figure R.5.1.1.2.5: 2 Time to first occurrence of sustained decline of >= 40% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.5.1.1.2.6 Time to first occurrence of sustained decline of >= 50% in eGFR

**Figure R.5.1.1.2.6: 1**

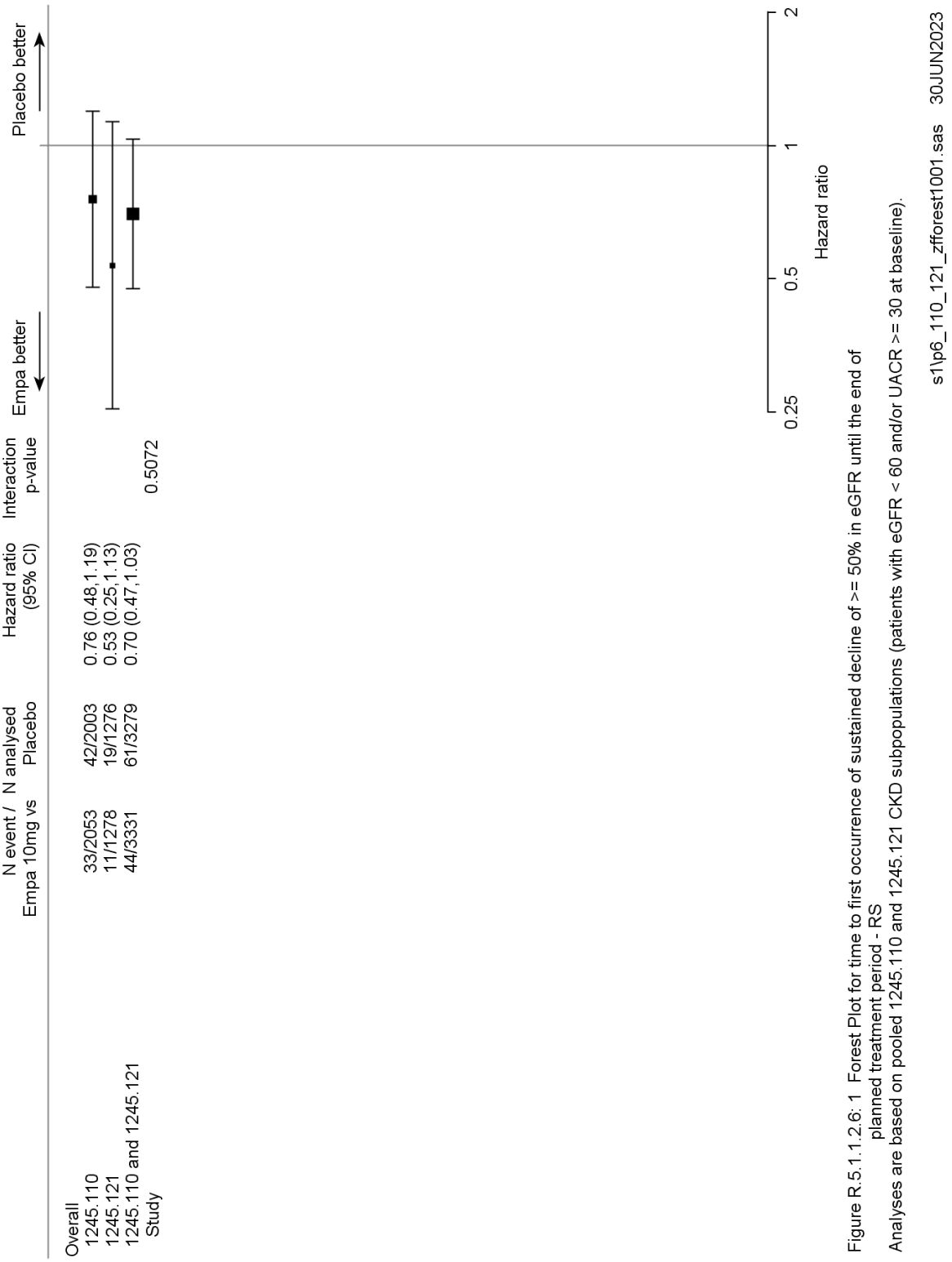


Figure R.5.1.1.2.6: 1 Forest Plot for time to first occurrence of sustained decline of >= 50% in eGFR until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.2.6: 1 Cox Regression for time to first occurrence of sustained decline of >= 50% in eGFR until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3279 | 61 | 1.9 | 1.32 | 3331 | 44 | 1.3 | 0.93 | 0.70 | (0.47,1.03) | 0.0716 | |
| Study | | | | | | | | | | | | 0.5072 |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, subgroup, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.2.6: 2**

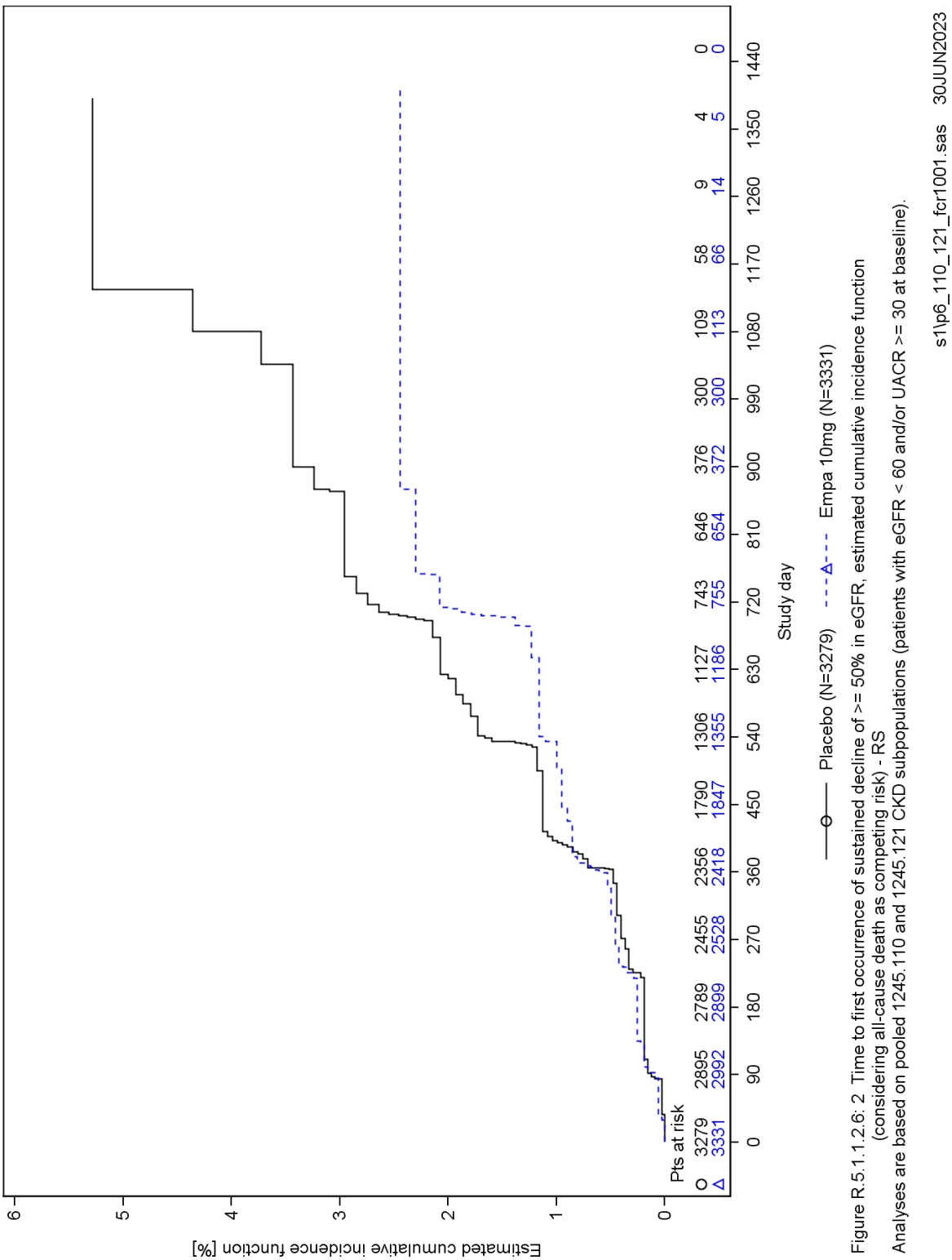


Figure R.5.1.1.2.6: 2 Time to first occurrence of sustained decline of >= 50% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.5.1.1.2.7

R.5.1.1.2.7 Time to first occurrence of sustained decline of >= 57% in eGFR

**Figure R.5.1.1.2.7: 1**

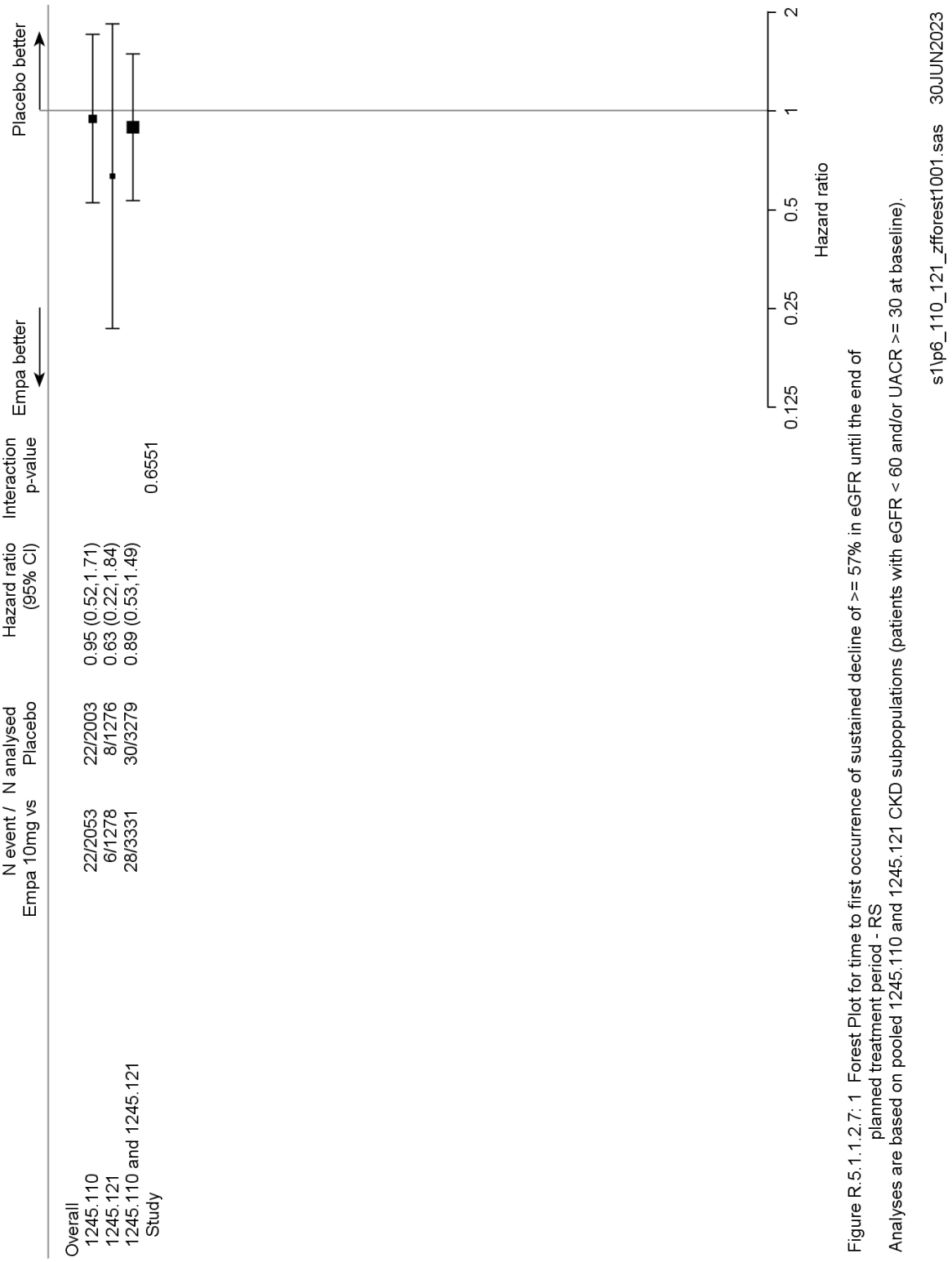


Figure R.5.1.1.2.7: 1 Forest Plot for time to first occurrence of sustained decline of >= 57% in eGFR until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.2.7: 1 Cox Regression for time to first occurrence of sustained decline of >= 57% in eGFR until the end of planned treatment period overall - RS

| Subgroup Category | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 30 | 0.9 | 0.65 | 3331 | 28 | 0.8 | 0.59 | 0.89 | (0.53,1.49) | 0.6595 | |
| Study | | | | | | | | | | | | 0.6551 |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, subgroup, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.2.7: 2**

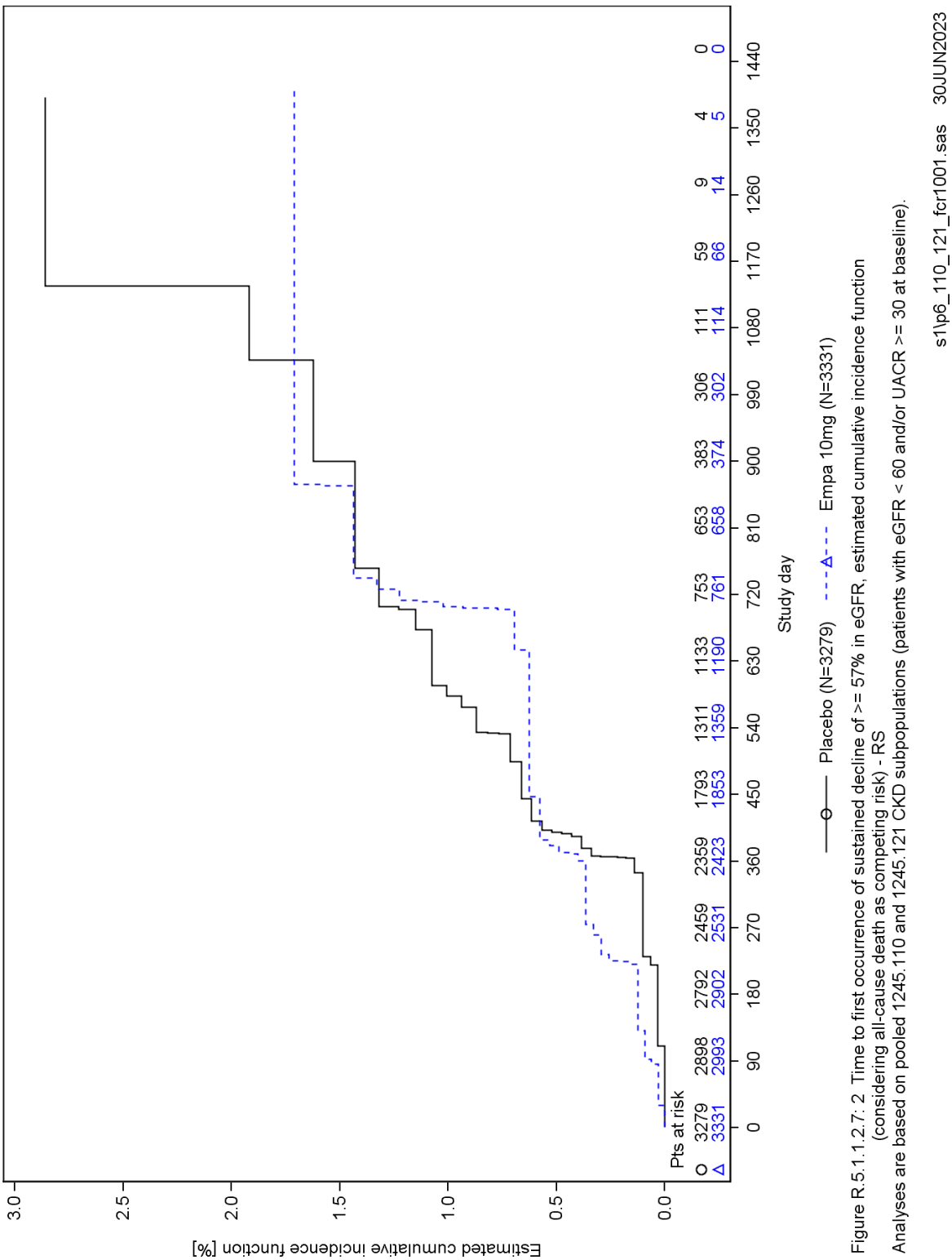


Figure R.5.1.1.2.7: 2 Time to first occurrence of sustained decline of >= 57% in eGFR, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**R.5.1.1.2.8**

R.5.1.1.2.8 Time to ESKD

**Figure R.5.1.1.2.8: 1**

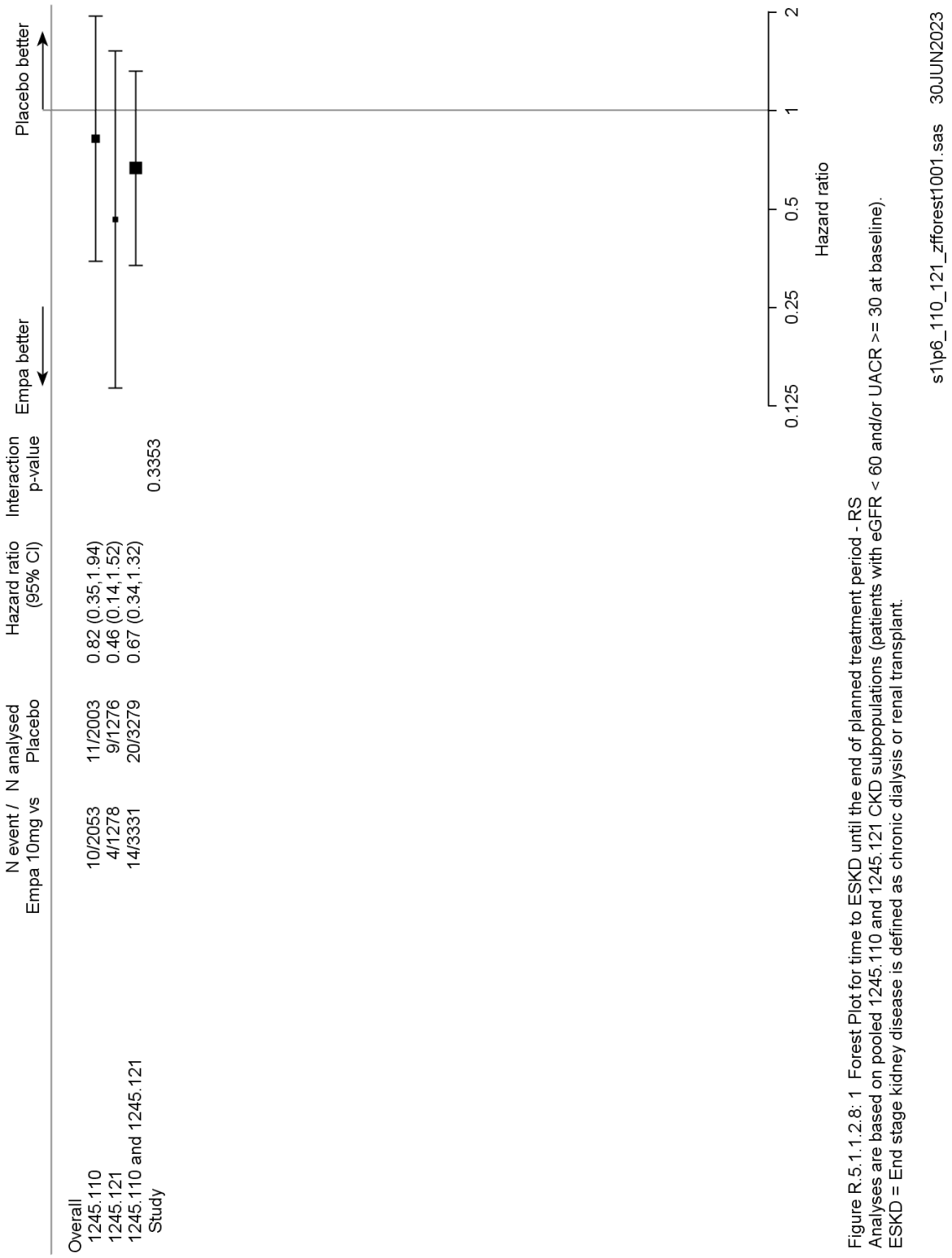


Figure R.5.1.1.2.8: 1 Forest Plot for time to ESKD until the end of planned treatment period - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

Table R.5.1.1.2.8: 1 Cox Regression for time to ESKD until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3279 | 20 | 0.6 | 0.34 | 3331 | 14 | 0.4 | 0.24 | 0.67 | (0.34,1.32) | 0.2437 | |
| Study | | | | | | | | | | | | 0.3353 |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, subgroup, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

**Figure R.5.1.1.2.8: 2**

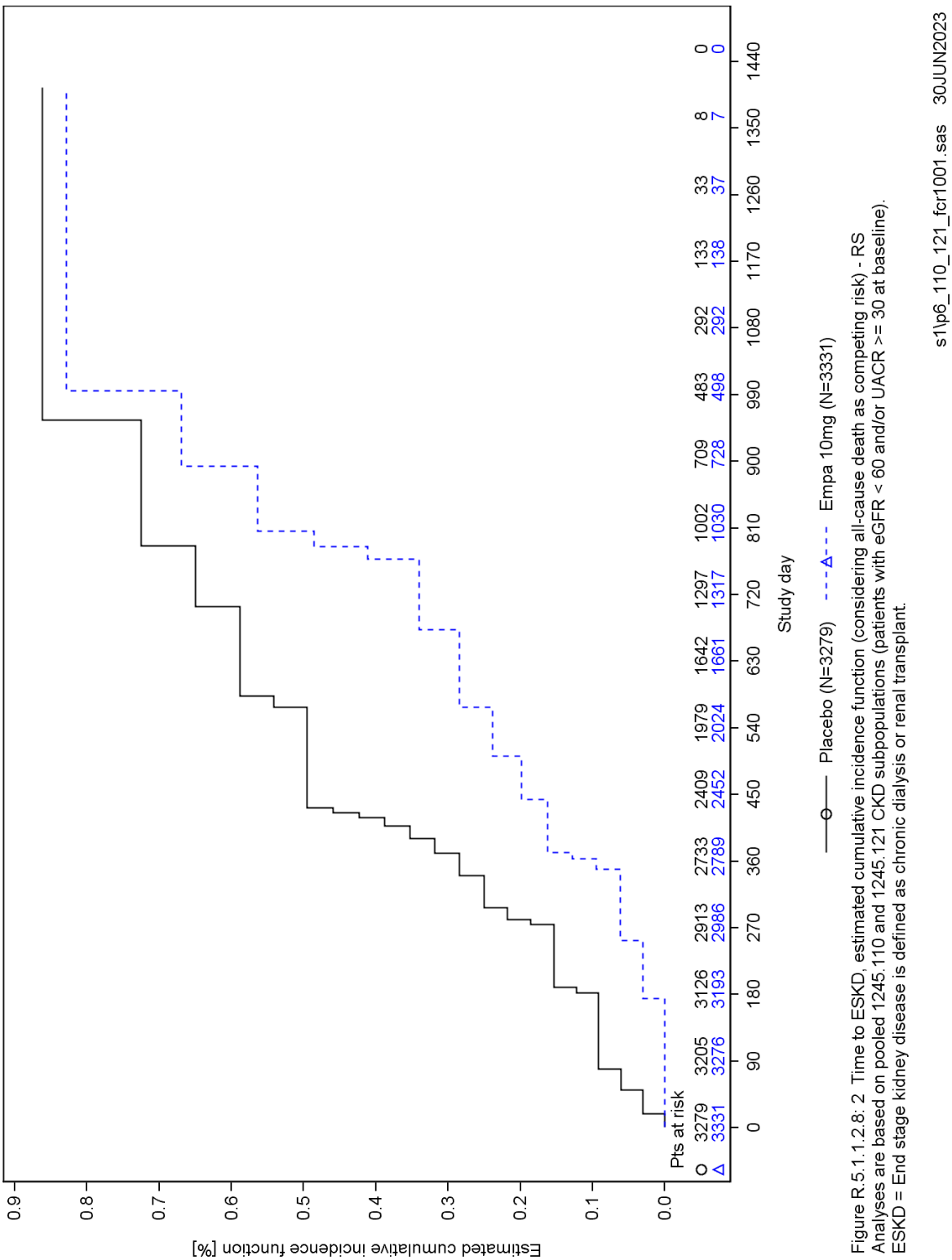


Figure R.5.1.1.2.8: 2 Time to ESKD, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

R.5.1.1.2.9 Time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death

**Figure R.5.1.1.2.9: 1**

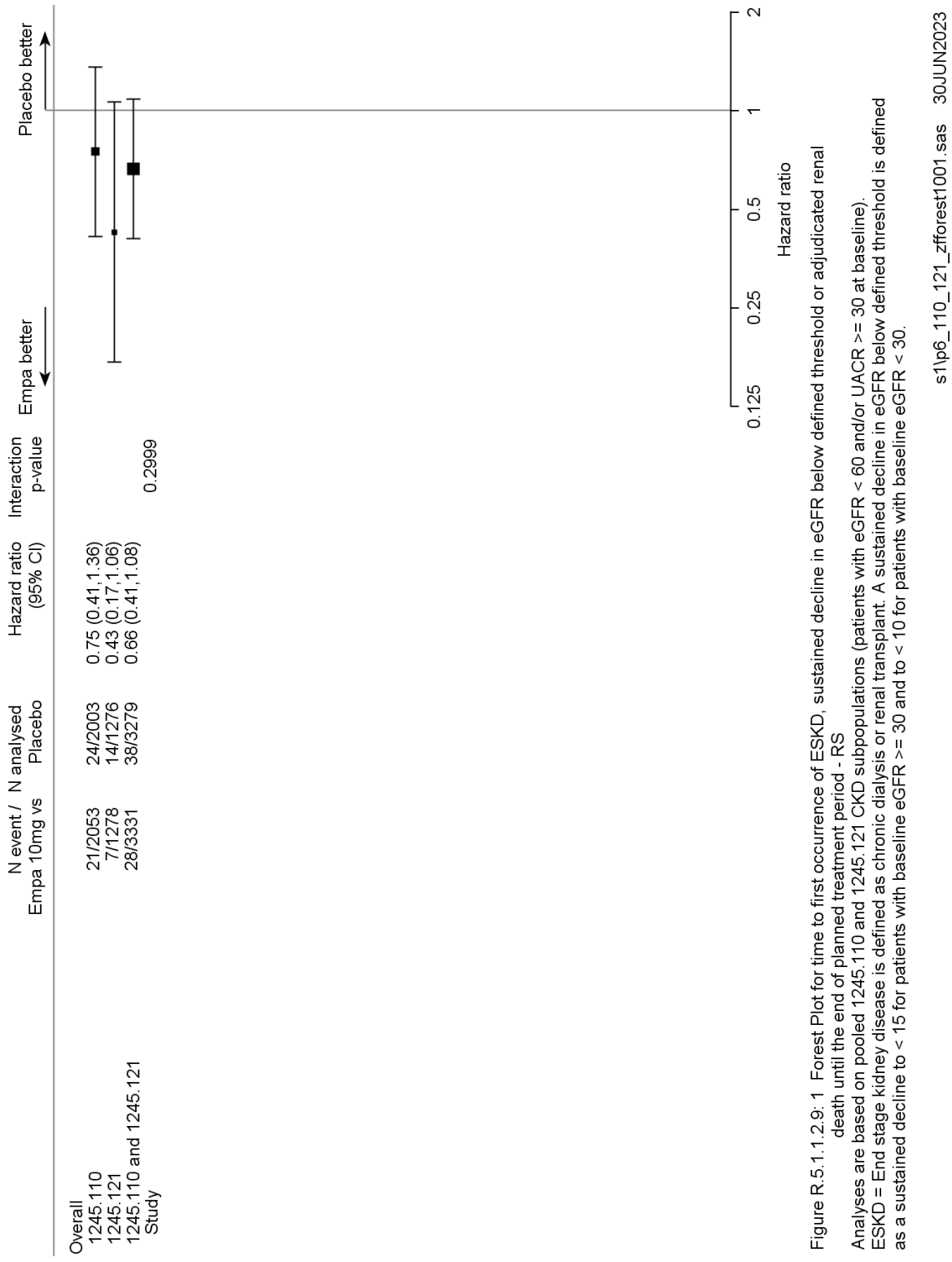


Figure R.5.1.1.2.9: 1 Forest Plot for time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

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Table R.5.1.1.2.9: 1 Cox Regression for time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 38 | 1.2 | 0.82 | 3331 | 28 | 0.8 | 0.59 | 0.66 | (0.41,1.08) | 0.1011 | |
| Study | | | | | | | | | | | | 0.2999 |
| Sex | | | | | | | | | | | | 0.4690 |
| Male | 2024 | 26 | 1.3 | 0.94 | 2069 | 22 | 1.1 | 0.77 | 0.74 | (0.42,1.31) | 0.3011 | |
| Female | 1255 | 12 | 1.0 | 0.64 | 1262 | 6 | 0.5 | 0.32 | 0.49 | (0.18,1.30) | 0.1505 | |
| Age [years] | | | | | | | | | | | | 0.7604 |
| <65 | 767 | 17 | 2.2 | 1.70 | 705 | 11 | 1.6 | 1.18 | 0.63 | (0.29,1.34) | 0.2277 | |
| >=65 | 2512 | 21 | 0.8 | 0.58 | 2626 | 17 | 0.6 | 0.44 | 0.73 | (0.38,1.39) | 0.3376 | |
| Region | | | | | | | | | | | | 0.8857 |
| North America | 434 | 10 | 2.3 | 1.64 | 433 | 10 | 2.3 | 1.56 | 0.90 | (0.37,2.16) | 0.8048 | |
| Latin America | 931 | 14 | 1.5 | 1.20 | 944 | 10 | 1.1 | 0.84 | 0.67 | (0.29,1.51) | 0.3293 | |
| Europe | 1338 | 9 | 0.7 | 0.45 | 1361 | 5 | 0.4 | 0.25 | 0.48 | (0.16,1.43) | 0.1885 | |
| Asia | 405 | 2 | 0.5 | 0.32 | 413 | 2 | 0.5 | 0.31 | 0.77 | (0.11,5.49) | 0.7942 | |
| Other | 171 | 3 | 1.8 | 1.21 | 180 | 1 | 0.6 | 0.40 | 0.34 | (0.03,3.23) | 0.3451 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3605 |
| Diabetic | 1742 | 28 | 1.6 | 1.16 | 1780 | 24 | 1.3 | 0.95 | 0.75 | (0.43,1.30) | 0.3052 | |
| Non-Diabetic | 1537 | 10 | 0.7 | 0.45 | 1551 | 4 | 0.3 | 0.18 | 0.41 | (0.13,1.32) | 0.1342 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9620 |
| <30 | 1977 | 20 | 1.0 | 0.74 | 1930 | 13 | 0.7 | 0.49 | 0.67 | (0.33,1.36) | 0.2708 | |
| >=30 | 1302 | 18 | 1.4 | 0.93 | 1401 | 15 | 1.1 | 0.72 | 0.66 | (0.33,1.31) | 0.2352 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0191 |
| <130 | 1686 | 21 | 1.2 | 0.94 | 1687 | 6 | 0.4 | 0.27 | 0.28 | (0.11,0.70) | 0.0065 | |
| >=130 | 1593 | 17 | 1.1 | 0.71 | 1644 | 22 | 1.3 | 0.88 | 1.07 | (0.56,2.03) | 0.8333 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7597 |
| <75 | 1656 | 20 | 1.2 | 0.88 | 1613 | 15 | 0.9 | 0.67 | 0.77 | (0.39,1.51) | 0.4515 | |
| 75 to <85 | 1006 | 11 | 1.1 | 0.74 | 1085 | 6 | 0.6 | 0.38 | 0.50 | (0.18,1.35) | 0.1695 | |
| >=85 | 617 | 7 | 1.1 | 0.80 | 633 | 7 | 1.1 | 0.74 | 0.60 | (0.21,1.76) | 0.3546 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

Table R.5.1.1.2.9: 1 Cox Regression for time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.9957 |
| <30 | 251 | 13 | 5.2 | 4.27 | 263 | 12 | 4.6 | 3.47 | 0.65 | (0.29,1.43) | 0.2847 | |
| 30 to <45 | 899 | 16 | 1.8 | 1.25 | 909 | 10 | 1.1 | 0.78 | 0.63 | (0.29,1.40) | 0.2602 | |
| >=45 | 2128 | 9 | 0.4 | 0.30 | 2159 | 6 | 0.3 | 0.19 | 0.67 | (0.24,1.90) | 0.4563 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.6932 |
| Normal (<30) | 1218 | 8 | 0.7 | 0.46 | 1243 | 4 | 0.3 | 0.22 | 0.50 | (0.15,1.66) | 0.2574 | |
| Microalbuminuria (30 to <=300) | 1549 | 14 | 0.9 | 0.64 | 1547 | 8 | 0.5 | 0.37 | 0.54 | (0.23,1.29) | 0.1639 | |
| Macroalbuminuria (>300) | 500 | 16 | 3.2 | 2.32 | 525 | 16 | 3.0 | 2.24 | 0.81 | (0.40,1.63) | 0.5529 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5463 |
| Low, moderate or high | 2432 | 11 | 0.5 | 0.32 | 2496 | 6 | 0.2 | 0.17 | 0.54 | (0.20,1.47) | 0.2301 | |
| Very high | 836 | 27 | 3.2 | 2.38 | 820 | 22 | 2.7 | 1.97 | 0.77 | (0.44,1.36) | 0.3724 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9620 |
| No | 573 | 10 | 1.7 | 1.21 | 579 | 7 | 1.2 | 0.80 | 0.65 | (0.25,1.72) | 0.3876 | |
| Yes | 2706 | 28 | 1.0 | 0.74 | 2752 | 21 | 0.8 | 0.54 | 0.67 | (0.38,1.19) | 0.1691 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4488 |
| No | 344 | 4 | 1.2 | 0.78 | 349 | 4 | 1.1 | 0.81 | 1.10 | (0.27,4.43) | 0.8890 | |
| Yes | 2935 | 34 | 1.2 | 0.83 | 2982 | 24 | 0.8 | 0.56 | 0.62 | (0.37,1.05) | 0.0768 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9808 |
| No | 275 | 2 | 0.7 | 0.45 | 307 | 0 | 0 | 0.00 | <0.01 | | 0.9803 | |
| Yes | 3004 | 36 | 1.2 | 0.86 | 3024 | 28 | 0.9 | 0.65 | 0.70 | (0.42,1.15) | 0.1580 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.5.1.1.2.9: 2**

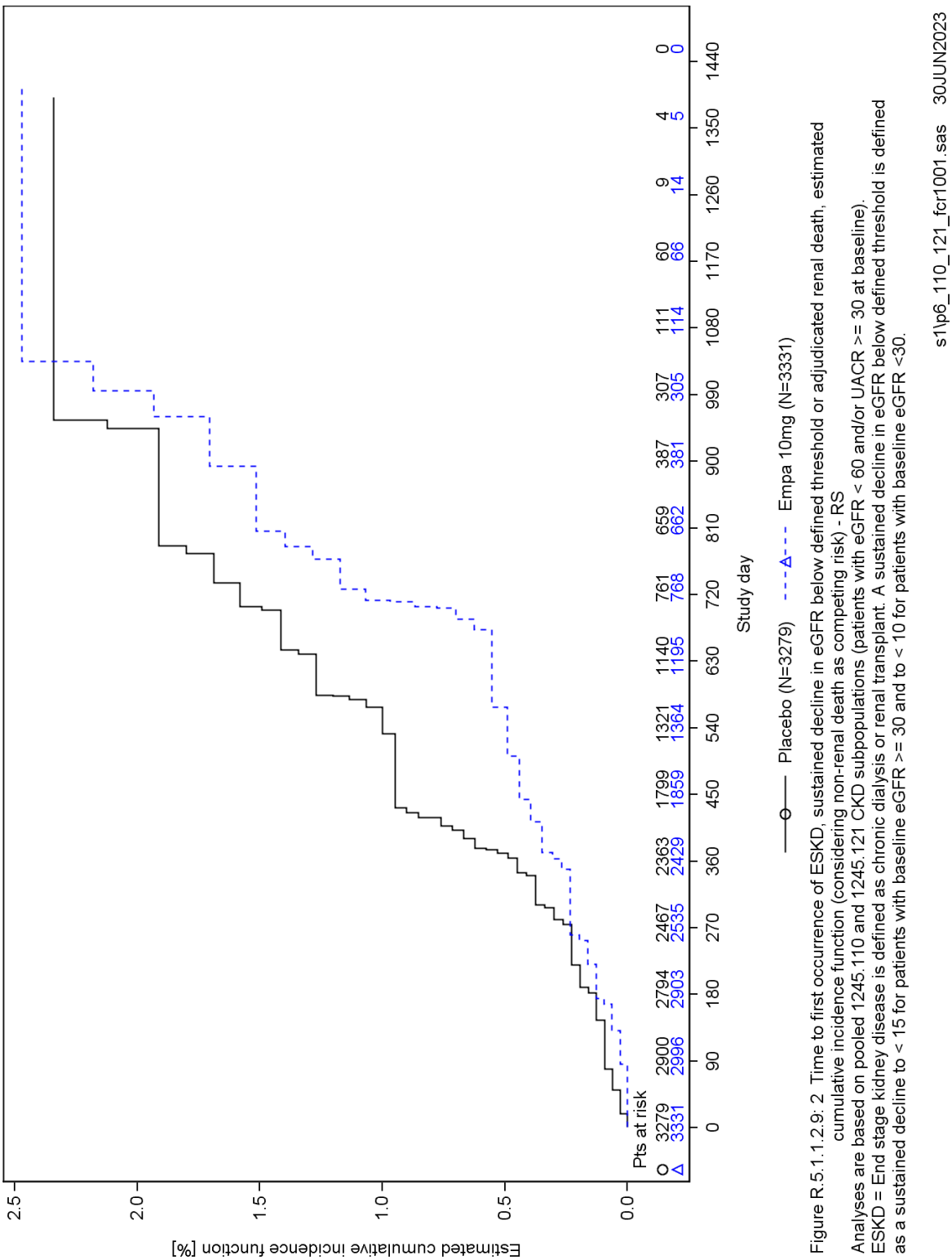


Figure R.5.1.1.2.9: 2 Time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death, estimated cumulative incidence function (considering non-renal death as competing risk) - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

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**Figure R.5.1.1.2.9: 3**

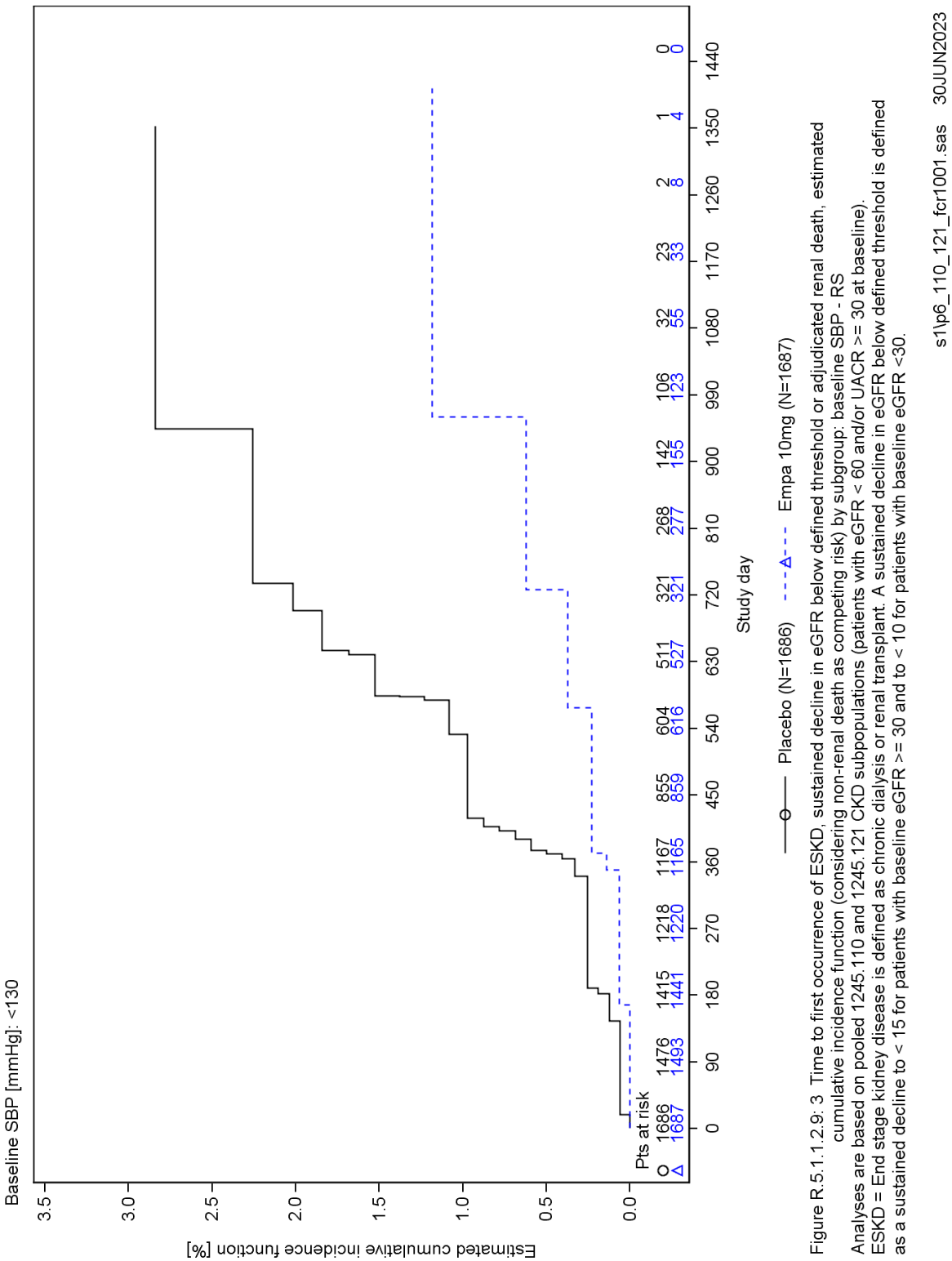


Figure R.5.1.1.2.9: 3 Time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death, estimated cumulative incidence function (considering non-renal death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

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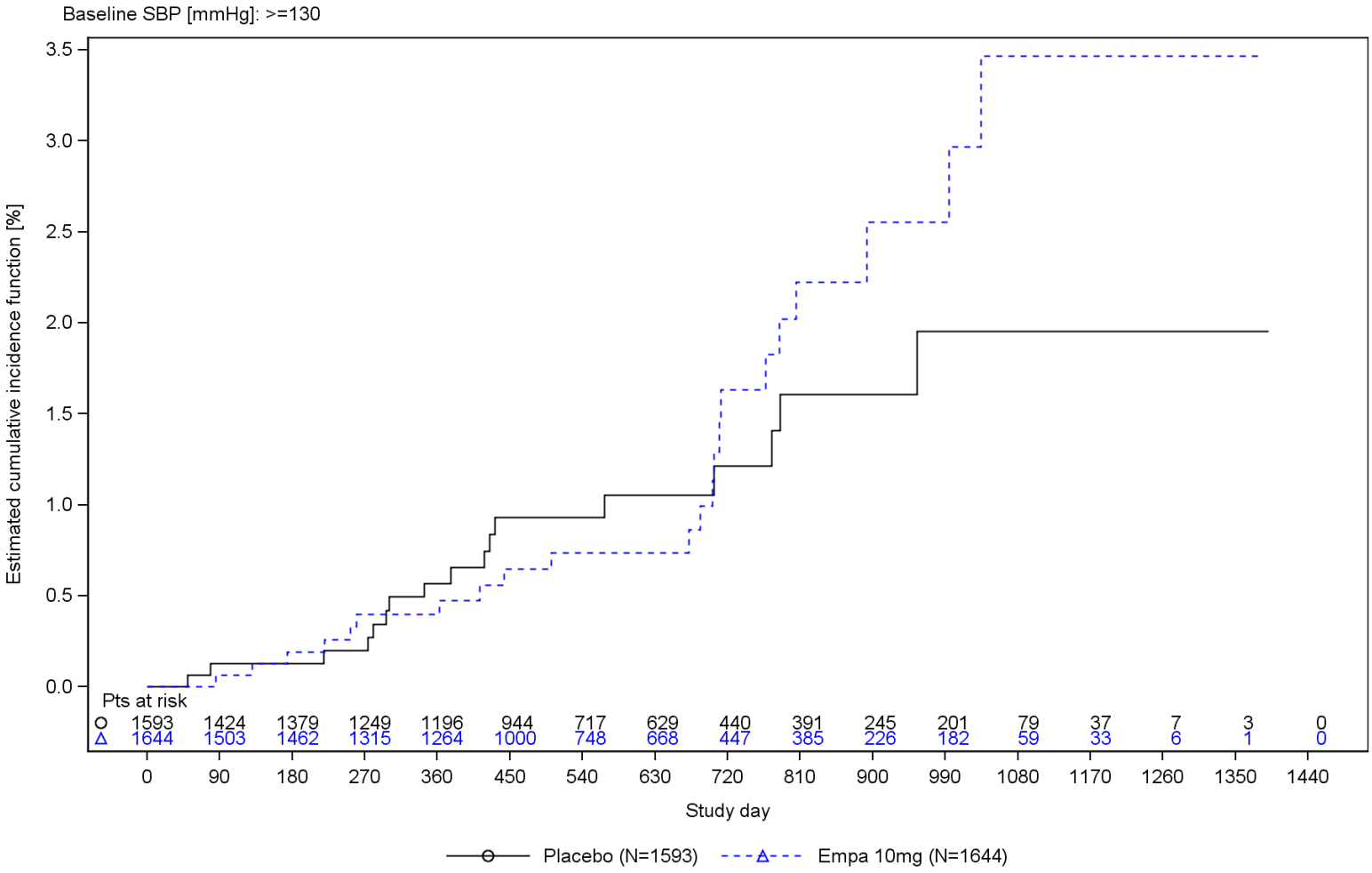


Figure R.5.1.1.2.9: 3 Time to first occurrence of ESKD, sustained decline in eGFR below defined threshold or adjudicated renal death, estimated cumulative incidence function (considering non-renal death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

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R.5.1.1.2.10 Time to first occurrence of ESKD or sustained decline in eGFR below defined threshold

**Figure R.5.1.1.2.10: 1**

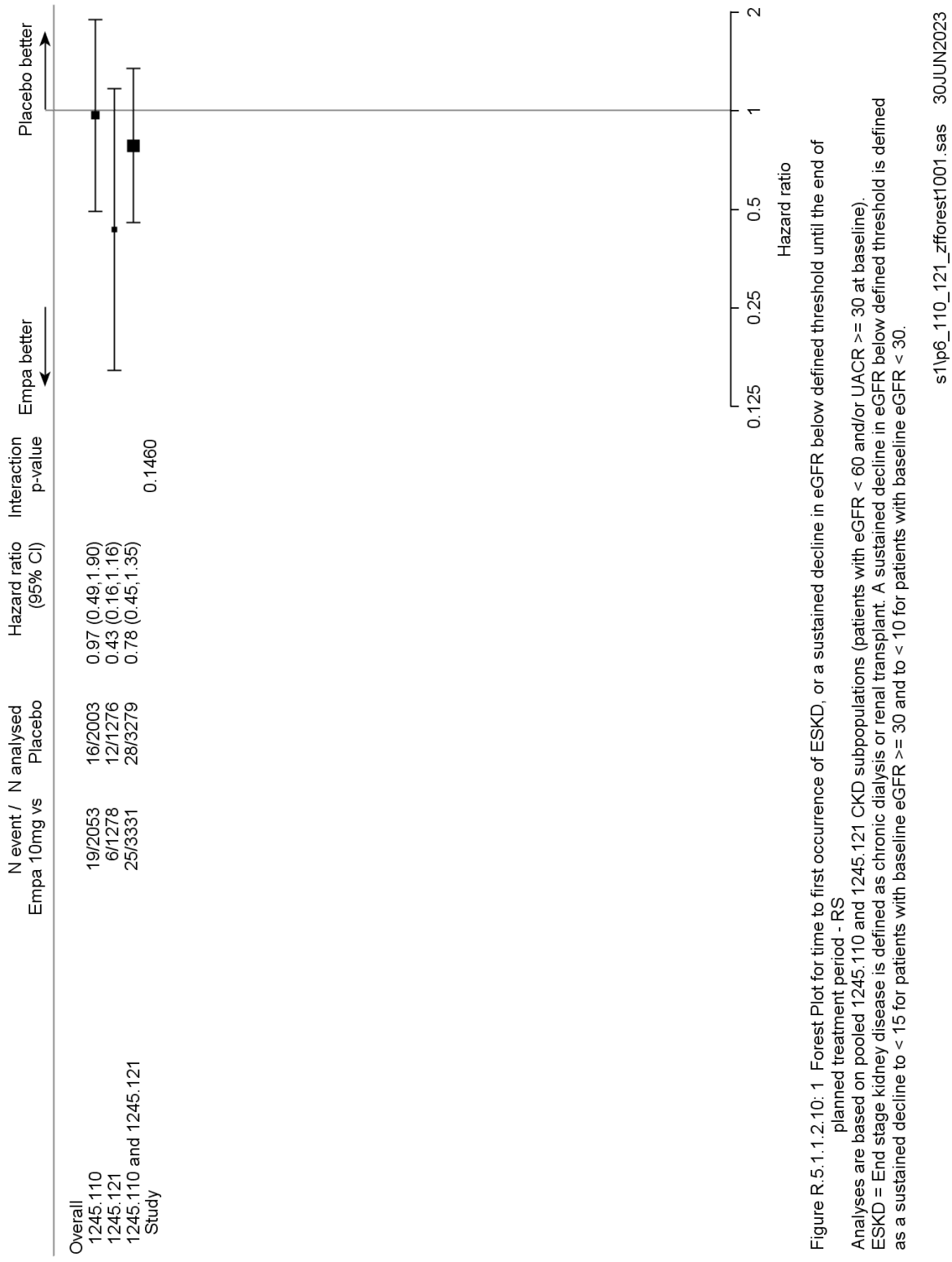


Figure R.5.1.1.2.10: 1 Forest Plot for time to first occurrence of ESKD, or a sustained decline in eGFR below defined threshold until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

Table R.5.1.1.2.10: 1 Cox Regression for time to first occurrence of ESKD or a sustained decline in eGFR below defined threshold until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 28 | 0.9 | 0.60 | 3331 | 25 | 0.8 | 0.52 | 0.78 | (0.45, 1.35) | 0.3737 | |
| Study | | | | | | | | | | | | 0.1460 |
| Sex | | | | | | | | | | | | 0.1044 |
| Male | 2024 | 16 | 0.8 | 0.58 | 2069 | 20 | 1.0 | 0.70 | 1.07 | (0.55, 2.07) | 0.8424 | |
| Female | 1255 | 12 | 1.0 | 0.64 | 1262 | 5 | 0.4 | 0.26 | 0.38 | (0.13, 1.09) | 0.0728 | |
| Age [years] | | | | | | | | | | | | 0.7462 |
| <65 | 767 | 12 | 1.6 | 1.20 | 705 | 9 | 1.3 | 0.96 | 0.72 | (0.30, 1.72) | 0.4610 | |
| >=65 | 2512 | 16 | 0.6 | 0.44 | 2626 | 16 | 0.6 | 0.42 | 0.87 | (0.43, 1.74) | 0.6871 | |
| Region | | | | | | | | | | | | 0.8191 |
| North America | 434 | 9 | 2.1 | 1.47 | 433 | 9 | 2.1 | 1.41 | 0.88 | (0.35, 2.23) | 0.7937 | |
| Latin America | 931 | 9 | 1.0 | 0.77 | 944 | 10 | 1.1 | 0.84 | 0.99 | (0.40, 2.45) | 0.9765 | |
| Europe | 1338 | 8 | 0.6 | 0.40 | 1361 | 4 | 0.3 | 0.20 | 0.43 | (0.13, 1.44) | 0.1719 | |
| Asia | 405 | 1 | 0.2 | 0.16 | 413 | 2 | 0.5 | 0.31 | 1.55 | (0.14,17.12) | 0.7223 | |
| Other | 171 | 1 | 0.6 | 0.41 | 180 | 0 | 0 | 0.00 | <0.01 | | 0.9842 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3314 |
| Diabetic | 1742 | 21 | 1.2 | 0.87 | 1780 | 22 | 1.2 | 0.87 | 0.89 | (0.49, 1.62) | 0.7010 | |
| Non-Diabetic | 1537 | 7 | 0.5 | 0.32 | 1551 | 3 | 0.2 | 0.13 | 0.43 | (0.11, 1.65) | 0.2170 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5709 |
| <30 | 1977 | 13 | 0.7 | 0.48 | 1930 | 12 | 0.6 | 0.45 | 0.93 | (0.42, 2.04) | 0.8475 | |
| >=30 | 1302 | 15 | 1.2 | 0.78 | 1401 | 13 | 0.9 | 0.62 | 0.68 | (0.32, 1.43) | 0.3052 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0361 |
| <130 | 1686 | 13 | 0.8 | 0.59 | 1687 | 4 | 0.2 | 0.18 | 0.29 | (0.09, 0.89) | 0.0298 | |
| >=130 | 1593 | 15 | 0.9 | 0.62 | 1644 | 21 | 1.3 | 0.84 | 1.17 | (0.60, 2.28) | 0.6497 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5605 |
| <75 | 1656 | 14 | 0.8 | 0.62 | 1613 | 14 | 0.9 | 0.63 | 1.00 | (0.48, 2.11) | 0.9932 | |
| 75 to <85 | 1006 | 9 | 0.9 | 0.61 | 1085 | 5 | 0.5 | 0.32 | 0.50 | (0.16, 1.49) | 0.2101 | |
| >=85 | 617 | 5 | 0.8 | 0.57 | 633 | 6 | 0.9 | 0.64 | 0.66 | (0.20, 2.24) | 0.5091 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

Table R.5.1.1.2.10: 1 Cox Regression for time to first occurrence of ESKD or a sustained decline in eGFR below defined threshold until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.9804 |
| <30 | 251 | 10 | 4.0 | 3.30 | 263 | 11 | 4.2 | 3.18 | 0.77 | (0.32, 1.82) | 0.5456 | |
| 30 to <45 | 899 | 11 | 1.2 | 0.86 | 909 | 9 | 1.0 | 0.70 | 0.82 | (0.34, 1.99) | 0.6666 | |
| >=45 | 2128 | 7 | 0.3 | 0.23 | 2159 | 5 | 0.2 | 0.16 | 0.71 | (0.23, 2.25) | 0.5629 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.4517 |
| Normal (<30) | 1218 | 6 | 0.5 | 0.34 | 1243 | 2 | 0.2 | 0.11 | 0.32 | (0.07, 1.61) | 0.1679 | |
| Microalbuminuria (30 to <=300) | 1549 | 10 | 0.6 | 0.46 | 1547 | 8 | 0.5 | 0.37 | 0.73 | (0.29, 1.86) | 0.5100 | |
| Macroalbuminuria (>300) | 500 | 12 | 2.4 | 1.75 | 525 | 15 | 2.9 | 2.10 | 1.00 | (0.46, 2.17) | 0.9913 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3260 |
| Low, moderate or high | 2432 | 8 | 0.3 | 0.23 | 2496 | 4 | 0.2 | 0.11 | 0.50 | (0.15, 1.65) | 0.2523 | |
| Very high | 836 | 20 | 2.4 | 1.76 | 820 | 21 | 2.6 | 1.88 | 0.97 | (0.53, 1.80) | 0.9349 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.9266 |
| No | 573 | 8 | 1.4 | 0.97 | 579 | 7 | 1.2 | 0.80 | 0.82 | (0.30, 2.28) | 0.7058 | |
| Yes | 2706 | 20 | 0.7 | 0.53 | 2752 | 18 | 0.7 | 0.46 | 0.78 | (0.41, 1.48) | 0.4387 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4060 |
| No | 344 | 1 | 0.3 | 0.19 | 349 | 2 | 0.6 | 0.40 | 2.09 | (0.19,23.17) | 0.5488 | |
| Yes | 2935 | 27 | 0.9 | 0.66 | 2982 | 23 | 0.8 | 0.54 | 0.73 | (0.42, 1.28) | 0.2765 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.9839 |
| No | 275 | 1 | 0.4 | 0.22 | 307 | 0 | 0 | 0.00 | <0.01 | | 0.9836 | |
| Yes | 3004 | 27 | 0.9 | 0.65 | 3024 | 25 | 0.8 | 0.58 | 0.81 | (0.47, 1.40) | 0.4432 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.5.1.1.2.10: 2**

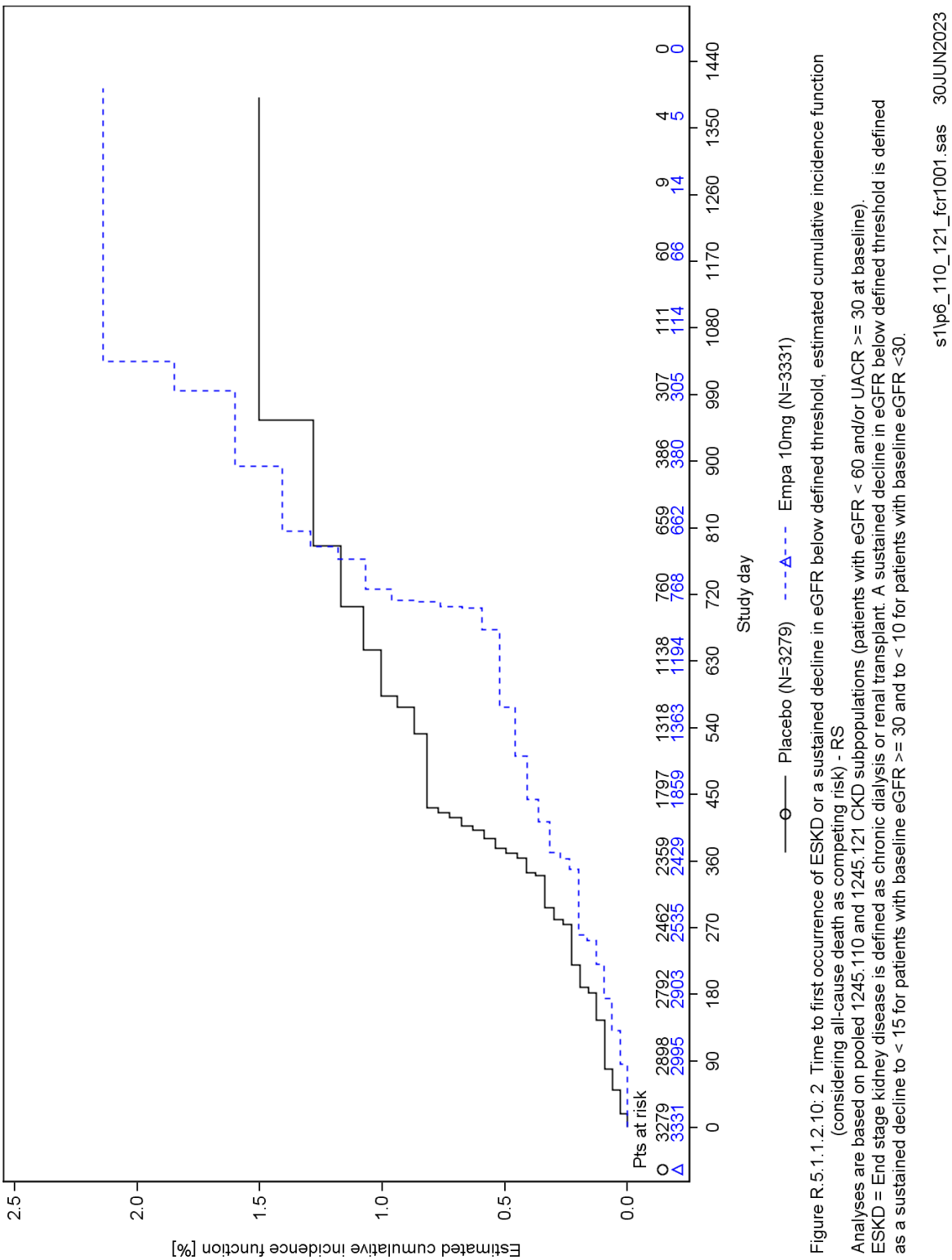


Figure R.5.1.1.2.10: 2 Time to first occurrence of ESKD or a sustained decline in eGFR below defined threshold, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

**Figure R.5.1.1.2.10: 3**

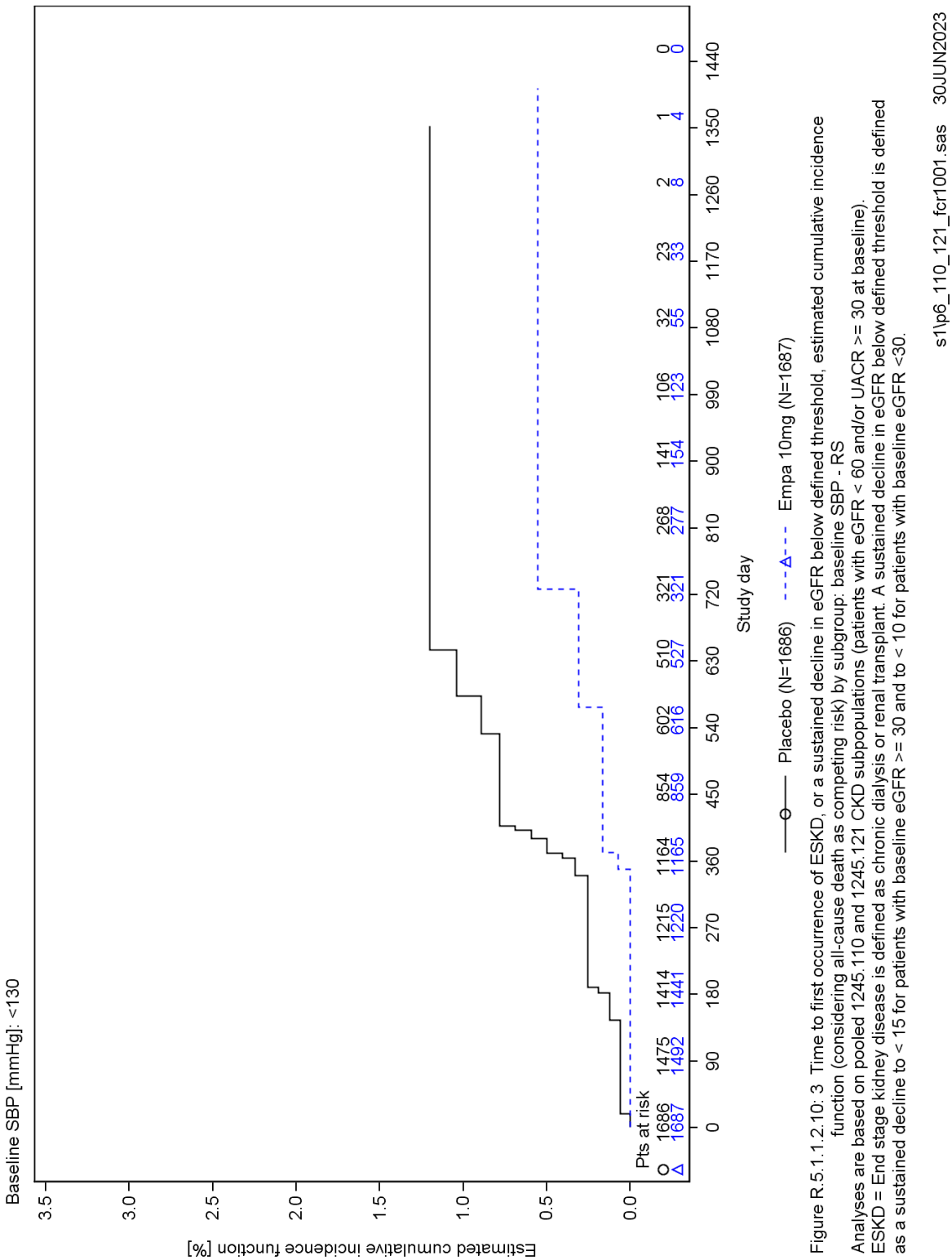


Figure R.5.1.1.2.10: 3 Time to first occurrence of ESKD, or a sustained decline in eGFR below defined threshold, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

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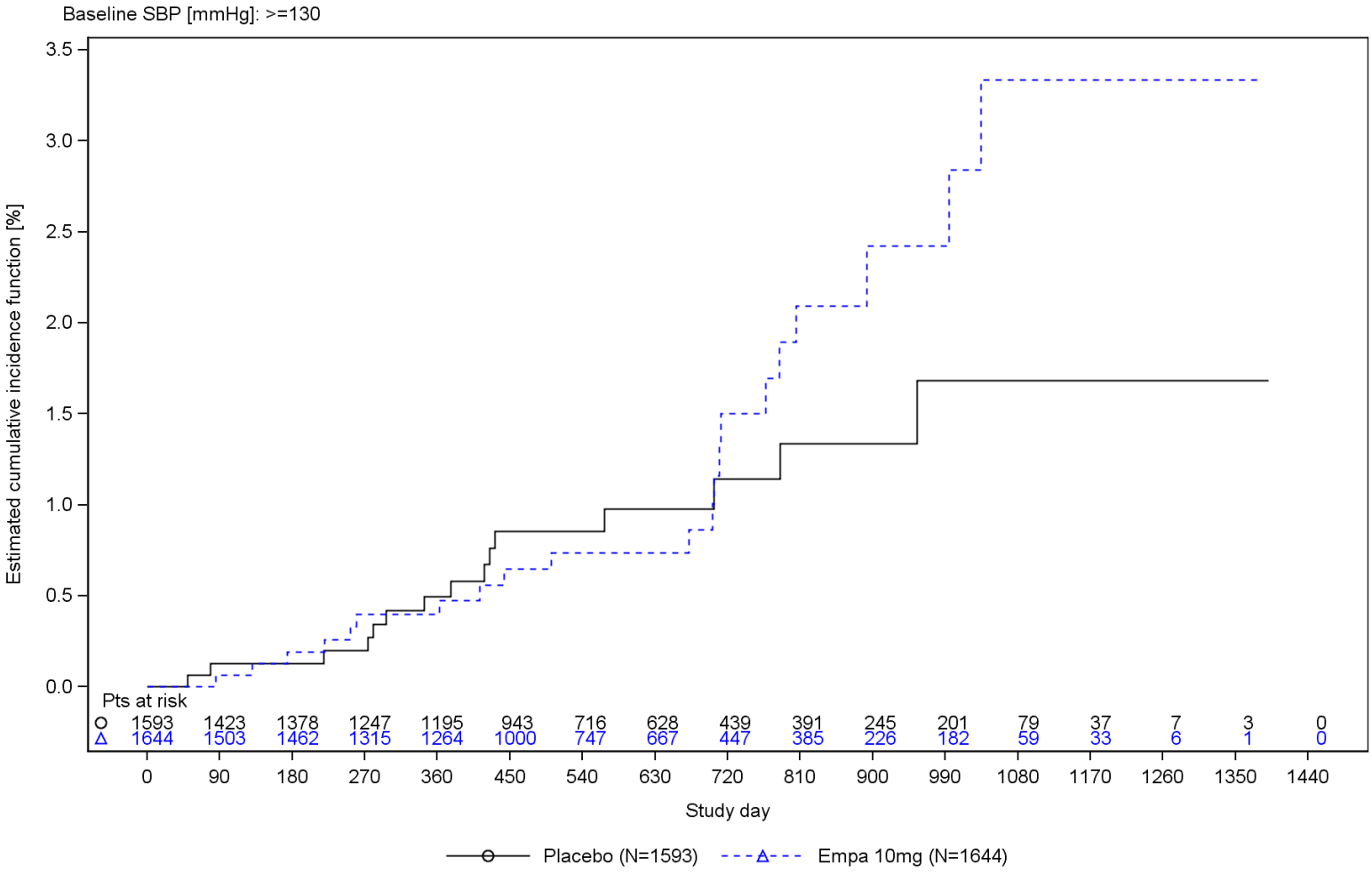


Figure R.5.1.1.2.10: 3 Time to first occurrence of ESKD, or a sustained decline in eGFR below defined threshold, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline SBP - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant. A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

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R.5.1.1.2.11 Time to first occurrence of sustained decline in eGFR below defined threshold

**Figure R.5.1.1.2.11: 1**

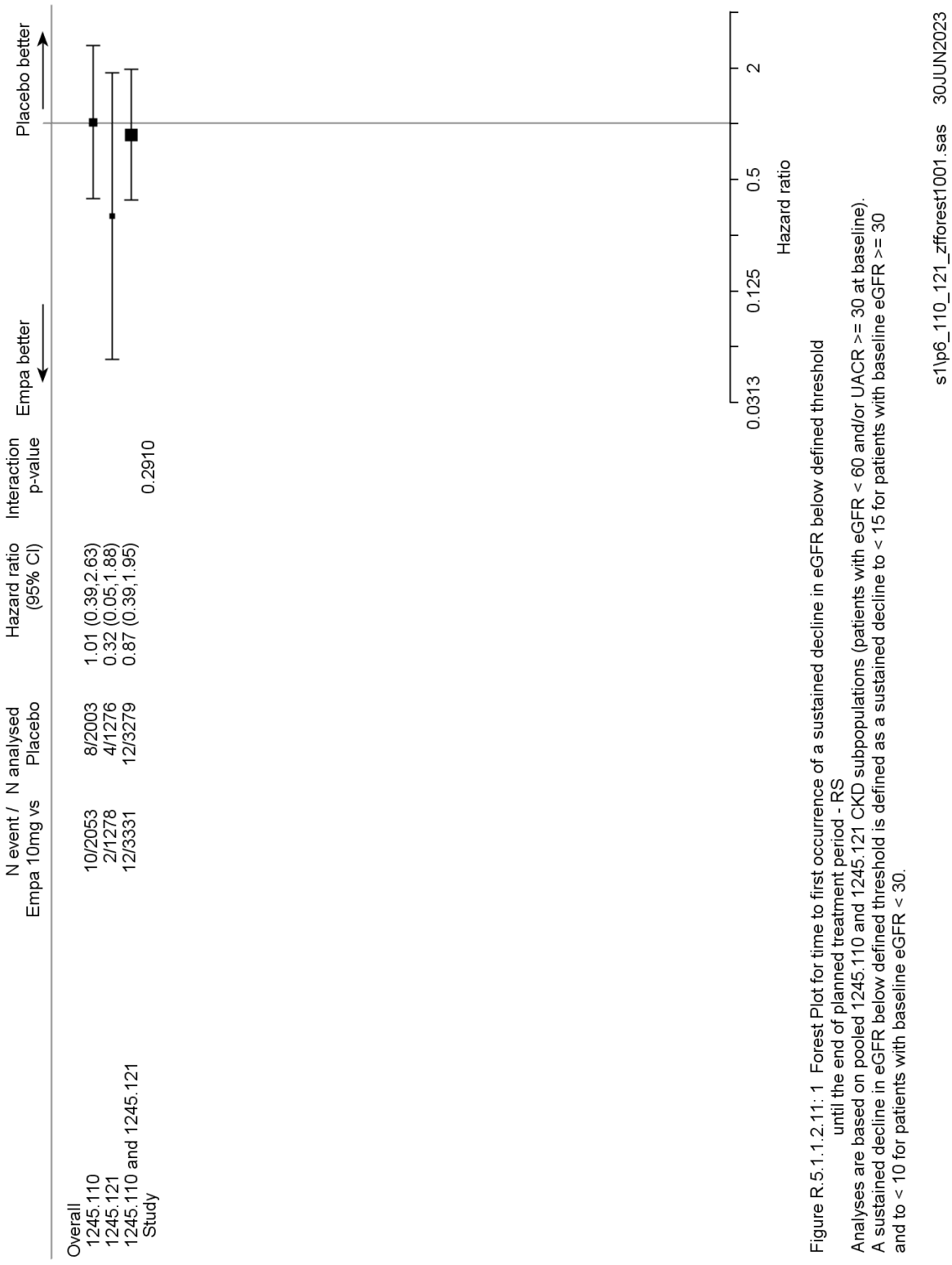


Figure R.5.1.1.2.11: 1 Forest Plot for time to first occurrence of a sustained decline in eGFR below defined threshold until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

Table R.5.1.1.2.11: 1 Cox Regression for time to first occurrence of a sustained decline in eGFR below defined threshold until the end of planned treatment period overall - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 12 | 0.4 | 0.26 | 3331 | 12 | 0.4 | 0.25 | 0.87 | (0.39,1.95) | 0.7333 | |
| Study | | | | | | | | | | | | 0.2910 |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, subgroup, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR < 30.

**Figure R.5.1.1.2.11: 2**

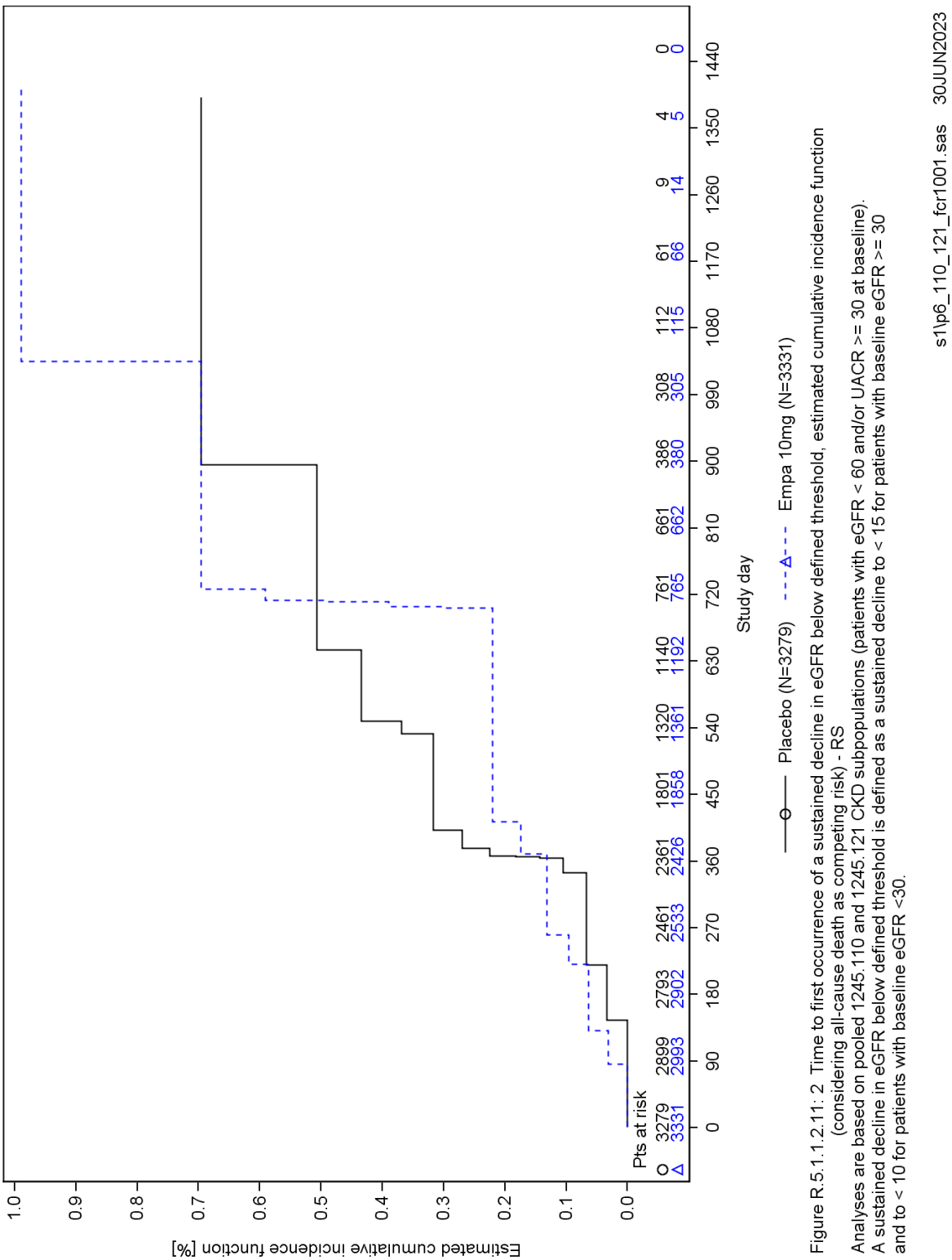


Figure R.5.1.1.2.11: 2 Time to first occurrence of a sustained decline in eGFR below defined threshold, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A sustained decline in eGFR below defined threshold is defined as a sustained decline to < 15 for patients with baseline eGFR >= 30 and to < 10 for patients with baseline eGFR <30.

R.5.1.1.2.12 Time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2

**Figure R.5.1.1.2.12: 1**

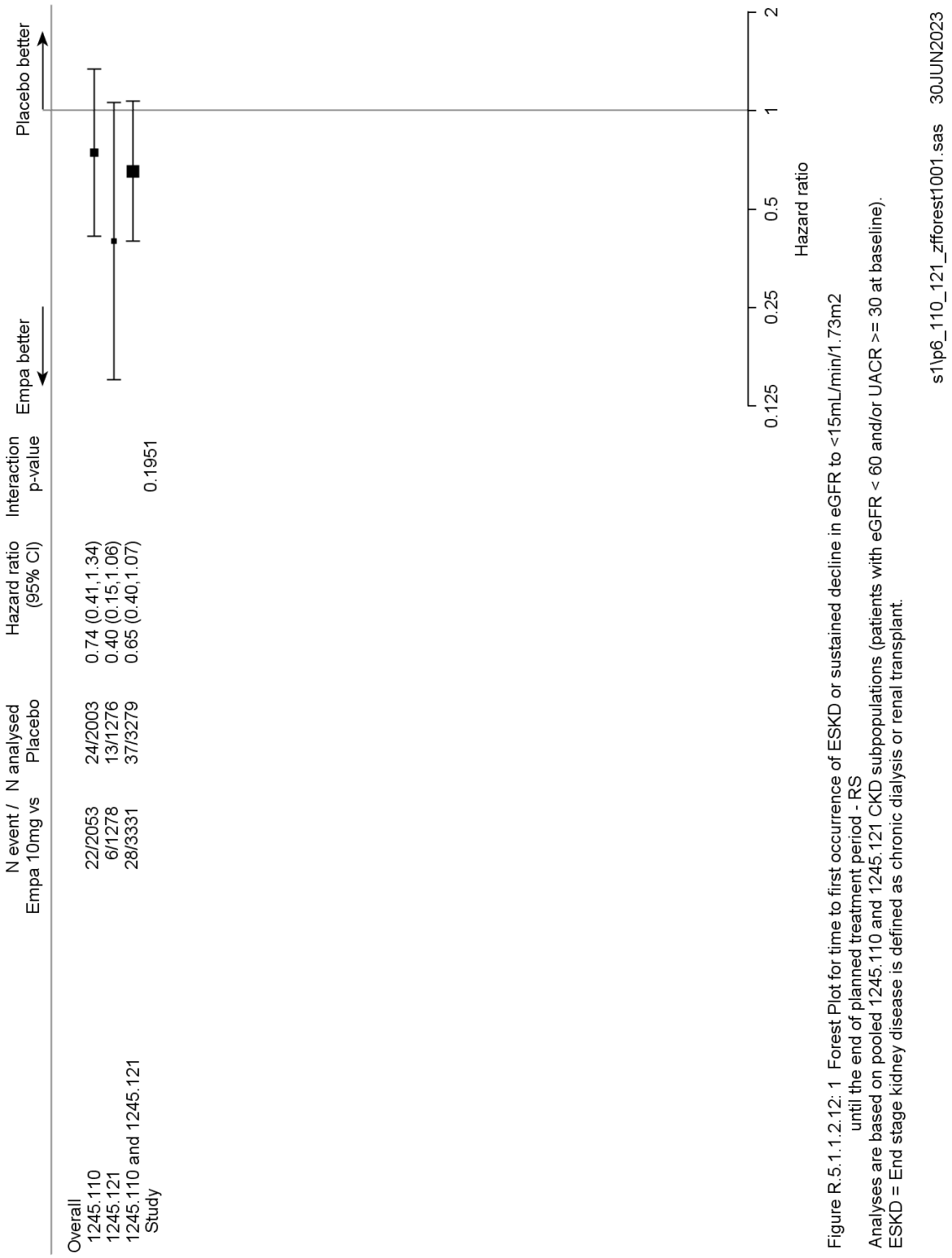


Figure R.5.1.1.2.12: 1 Forest Plot for time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2 until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

Table R.5.1.1.2.12: 1 Cox Regression for time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2 until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 37 | 1.1 | 0.80 | 3331 | 28 | 0.8 | 0.59 | 0.65 | (0.40, 1.07) | 0.0900 | |
| Study | | | | | | | | | | | | 0.1951 |
| Sex | | | | | | | | | | | | 0.1022 |
| Male | 2024 | 23 | 1.1 | 0.83 | 2069 | 23 | 1.1 | 0.80 | 0.85 | (0.47, 1.52) | 0.5865 | |
| Female | 1255 | 14 | 1.1 | 0.75 | 1262 | 5 | 0.4 | 0.26 | 0.32 | (0.11, 0.89) | 0.0286 | |
| Age [years] | | | | | | | | | | | | 0.8148 |
| <65 | 767 | 15 | 2.0 | 1.51 | 705 | 11 | 1.6 | 1.18 | 0.73 | (0.33, 1.59) | 0.4270 | |
| >=65 | 2512 | 22 | 0.9 | 0.61 | 2626 | 17 | 0.6 | 0.44 | 0.65 | (0.34, 1.22) | 0.1782 | |
| Region | | | | | | | | | | | | 0.9452 |
| North America | 434 | 11 | 2.5 | 1.81 | 433 | 9 | 2.1 | 1.41 | 0.74 | (0.30, 1.78) | 0.4973 | |
| Latin America | 931 | 13 | 1.4 | 1.11 | 944 | 11 | 1.2 | 0.92 | 0.75 | (0.33, 1.70) | 0.4959 | |
| Europe | 1338 | 9 | 0.7 | 0.45 | 1361 | 5 | 0.4 | 0.25 | 0.46 | (0.16, 1.39) | 0.1708 | |
| Asia | 405 | 2 | 0.5 | 0.32 | 413 | 3 | 0.7 | 0.46 | 1.02 | (0.17, 6.14) | 0.9848 | |
| Other | 171 | 2 | 1.2 | 0.82 | 180 | 0 | 0 | 0.00 | <0.01 | | 0.9803 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.4890 |
| Diabetic | 1742 | 28 | 1.6 | 1.16 | 1780 | 24 | 1.3 | 0.95 | 0.71 | (0.41, 1.23) | 0.2234 | |
| Non-Diabetic | 1537 | 9 | 0.6 | 0.41 | 1551 | 4 | 0.3 | 0.18 | 0.45 | (0.14, 1.46) | 0.1830 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.5846 |
| <30 | 1977 | 16 | 0.8 | 0.59 | 1930 | 13 | 0.7 | 0.49 | 0.76 | (0.36, 1.58) | 0.4569 | |
| >=30 | 1302 | 21 | 1.6 | 1.09 | 1401 | 15 | 1.1 | 0.72 | 0.57 | (0.29, 1.12) | 0.1028 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0235 |
| <130 | 1686 | 16 | 0.9 | 0.72 | 1687 | 4 | 0.2 | 0.18 | 0.23 | (0.08, 0.68) | 0.0079 | |
| >=130 | 1593 | 21 | 1.3 | 0.87 | 1644 | 24 | 1.5 | 0.96 | 0.96 | (0.53, 1.73) | 0.8859 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5555 |
| <75 | 1656 | 18 | 1.1 | 0.79 | 1613 | 15 | 0.9 | 0.67 | 0.80 | (0.40, 1.59) | 0.5250 | |
| 75 to <85 | 1006 | 11 | 1.1 | 0.75 | 1085 | 5 | 0.5 | 0.32 | 0.41 | (0.14, 1.18) | 0.0977 | |
| >=85 | 617 | 8 | 1.3 | 0.91 | 633 | 8 | 1.3 | 0.85 | 0.55 | (0.20, 1.50) | 0.2438 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

Table R.5.1.1.2.12: 1 Cox Regression for time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2 until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.7730 |
| <30 | 251 | 19 | 7.6 | 6.38 | 263 | 14 | 5.3 | 4.12 | 0.55 | (0.27, 1.10) | 0.0885 | |
| 30 to <45 | 899 | 11 | 1.2 | 0.86 | 909 | 9 | 1.0 | 0.70 | 0.81 | (0.34, 1.96) | 0.6451 | |
| >=45 | 2128 | 7 | 0.3 | 0.23 | 2159 | 5 | 0.2 | 0.16 | 0.71 | (0.23, 2.25) | 0.5669 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.6579 |
| Normal (<30) | 1218 | 6 | 0.5 | 0.34 | 1243 | 2 | 0.2 | 0.11 | 0.33 | (0.07, 1.62) | 0.1703 | |
| Microalbuminuria (30 to <=300) | 1549 | 11 | 0.7 | 0.50 | 1547 | 8 | 0.5 | 0.37 | 0.63 | (0.25, 1.58) | 0.3261 | |
| Macroalbuminuria (>300) | 500 | 20 | 4.0 | 2.94 | 525 | 18 | 3.4 | 2.54 | 0.73 | (0.38, 1.40) | 0.3401 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.5110 |
| Low, moderate or high | 2432 | 8 | 0.3 | 0.23 | 2496 | 4 | 0.2 | 0.11 | 0.50 | (0.15, 1.65) | 0.2531 | |
| Very high | 836 | 29 | 3.5 | 2.57 | 820 | 24 | 2.9 | 2.16 | 0.77 | (0.45, 1.33) | 0.3506 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.7983 |
| No | 573 | 11 | 1.9 | 1.34 | 579 | 7 | 1.2 | 0.80 | 0.59 | (0.23, 1.54) | 0.2787 | |
| Yes | 2706 | 26 | 1.0 | 0.68 | 2752 | 21 | 0.8 | 0.54 | 0.68 | (0.38, 1.22) | 0.1962 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.0773 |
| No | 344 | 1 | 0.3 | 0.19 | 349 | 4 | 1.1 | 0.81 | 4.29 | (0.48,38.59) | 0.1941 | |
| Yes | 2935 | 36 | 1.2 | 0.88 | 2982 | 24 | 0.8 | 0.56 | 0.56 | (0.33, 0.94) | 0.0294 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.7076 |
| No | 275 | 2 | 0.7 | 0.45 | 307 | 1 | 0.3 | 0.21 | 0.42 | (0.04, 4.66) | 0.4763 | |
| Yes | 3004 | 35 | 1.2 | 0.84 | 3024 | 27 | 0.9 | 0.63 | 0.67 | (0.40, 1.11) | 0.1162 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

**Figure R.5.1.1.2.12: 2**

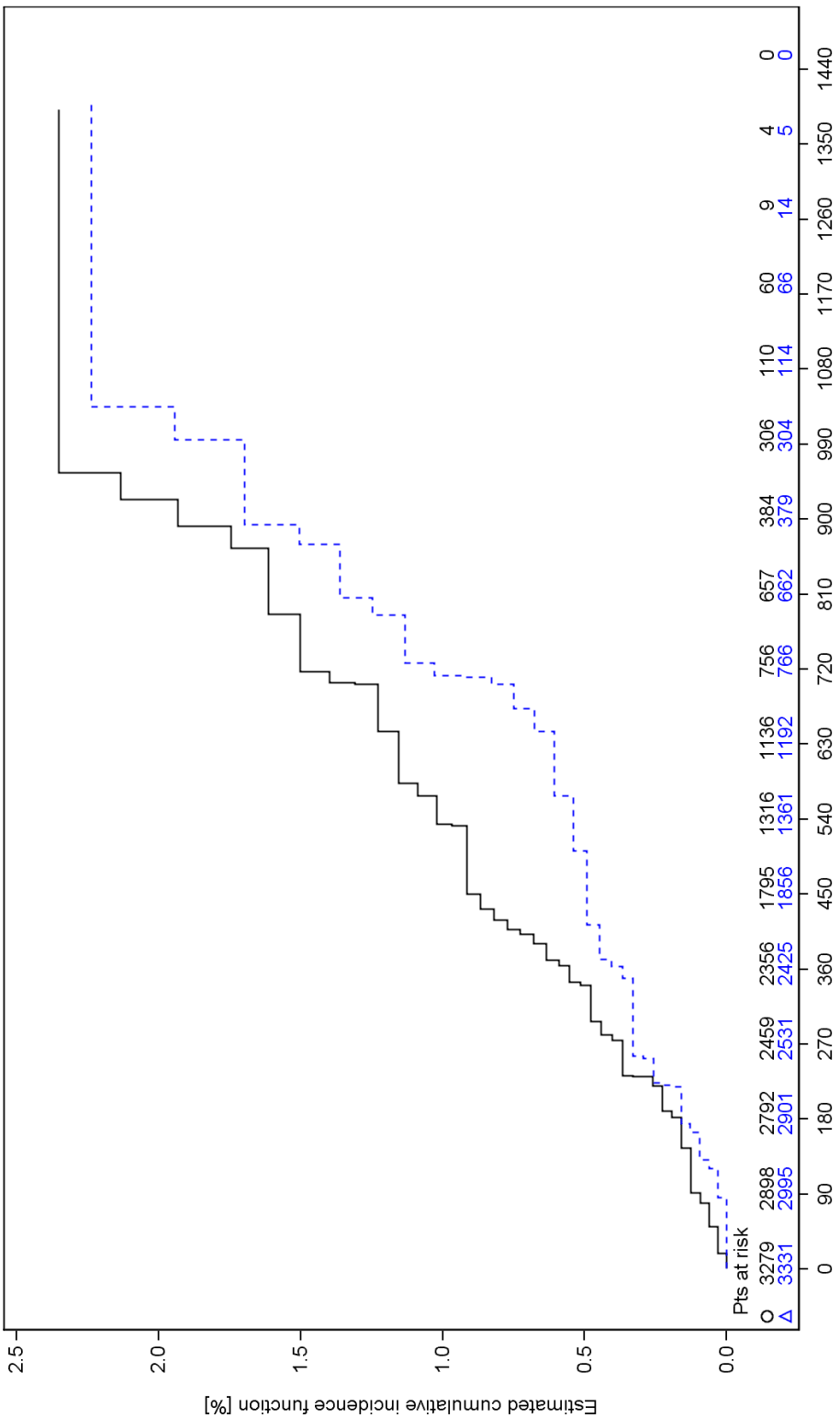


Figure R.5.1.1.2.12: 2 Time to first occurrence of ESKD or sustained decline in eGFR to <15mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

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**Figure R.5.1.1.2.12: 3**

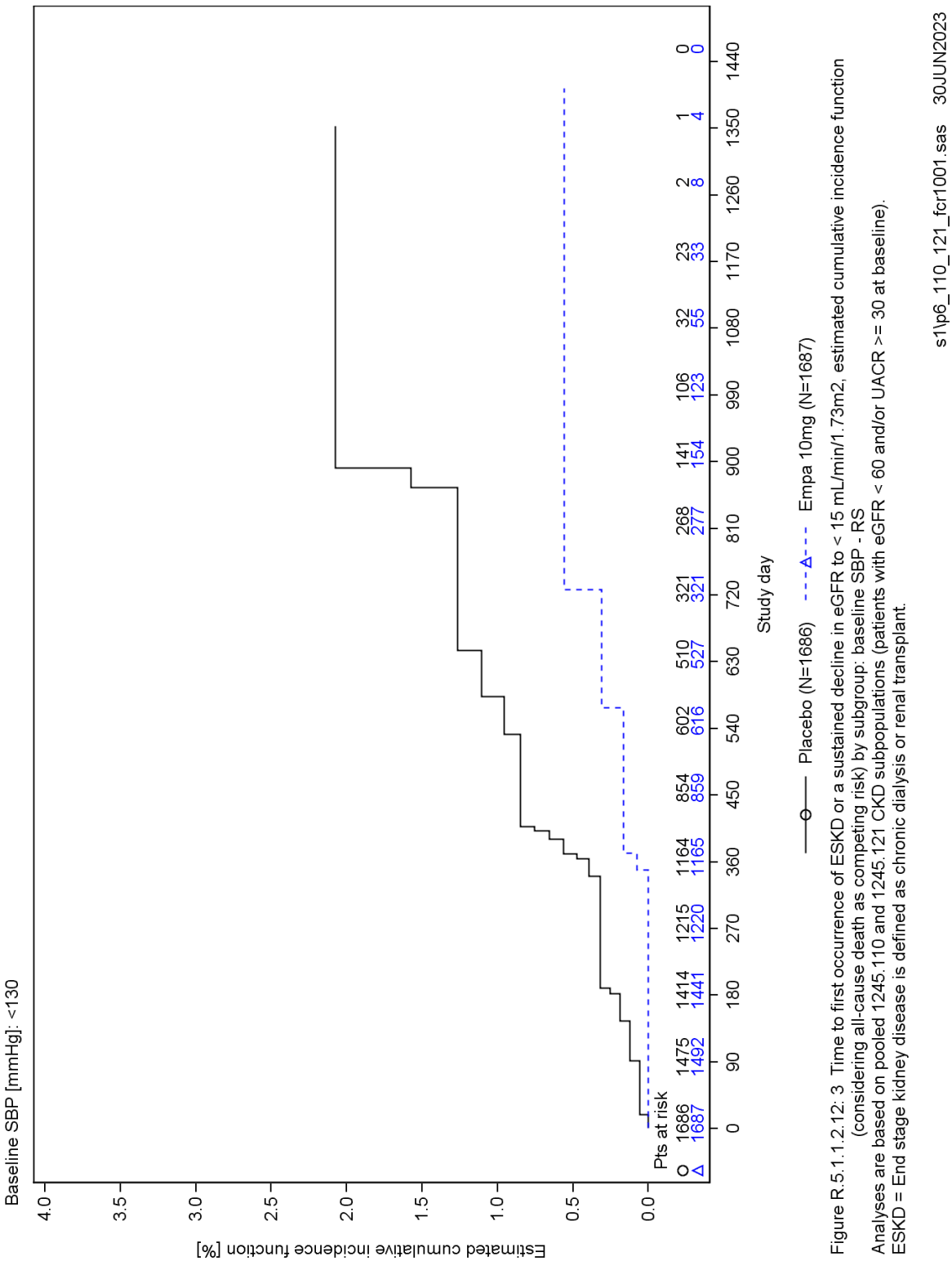


Figure R.5.1.1.2.12: 3 Time to first occurrence of ESKD or a sustained decline in eGFR to < 15 mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline SBP - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

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**Figure R.5.1.1.2.12: 3**

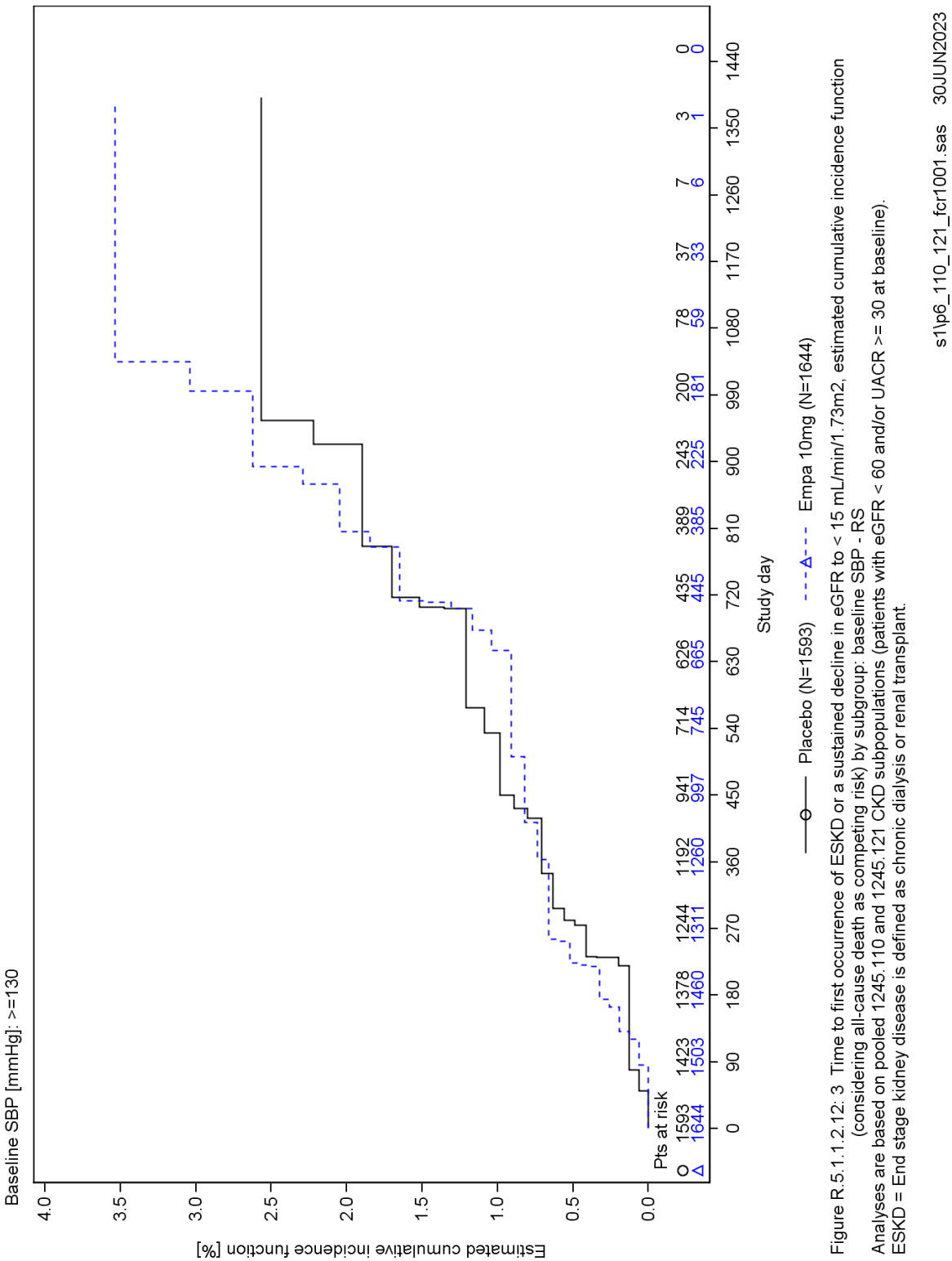


Figure R.5.1.1.2.12: 3 Time to first occurrence of ESKD or a sustained decline in eGFR to < 15 mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline SBP - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
ESKD = End stage kidney disease is defined as chronic dialysis or renal transplant.

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R.5.1.1.2.13 Time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2

**Figure R.5.1.1.2.13: 1**

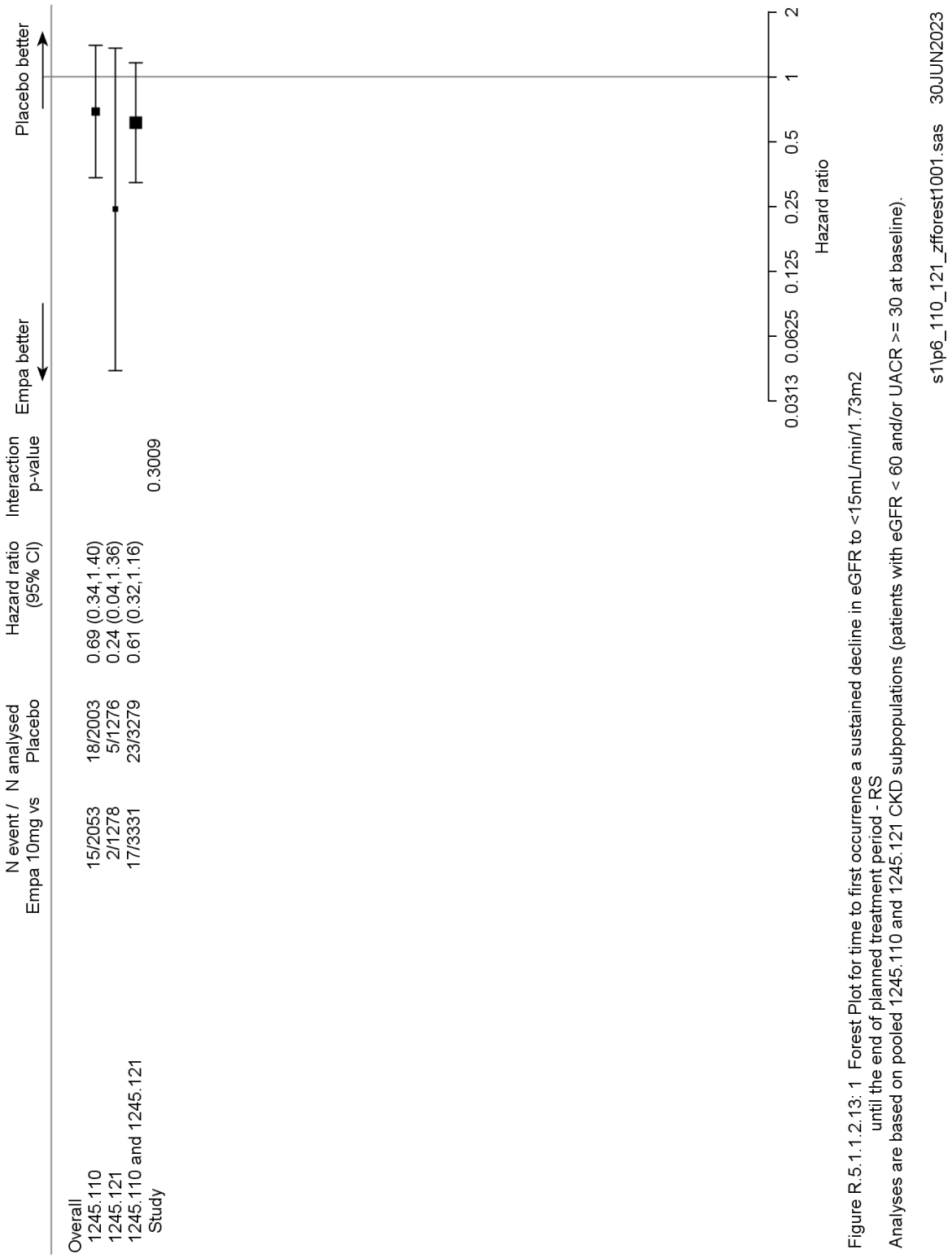


Figure R.5.1.1.2.13: 1 Forest Plot for time to first occurrence a sustained decline in eGFR to <15mL/min/1.73m2 until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.2.13: 1 Cox Regression for time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2 until the end of planned treatment period overall - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3279 | 23 | 0.7 | 0.50 | 3331 | 17 | 0.5 | 0.36 | 0.61 | (0.32,1.16) | 0.1324 | |
| Study | | | | | | | | | | | | 0.3009 |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, subgroup, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.2.13: 2**

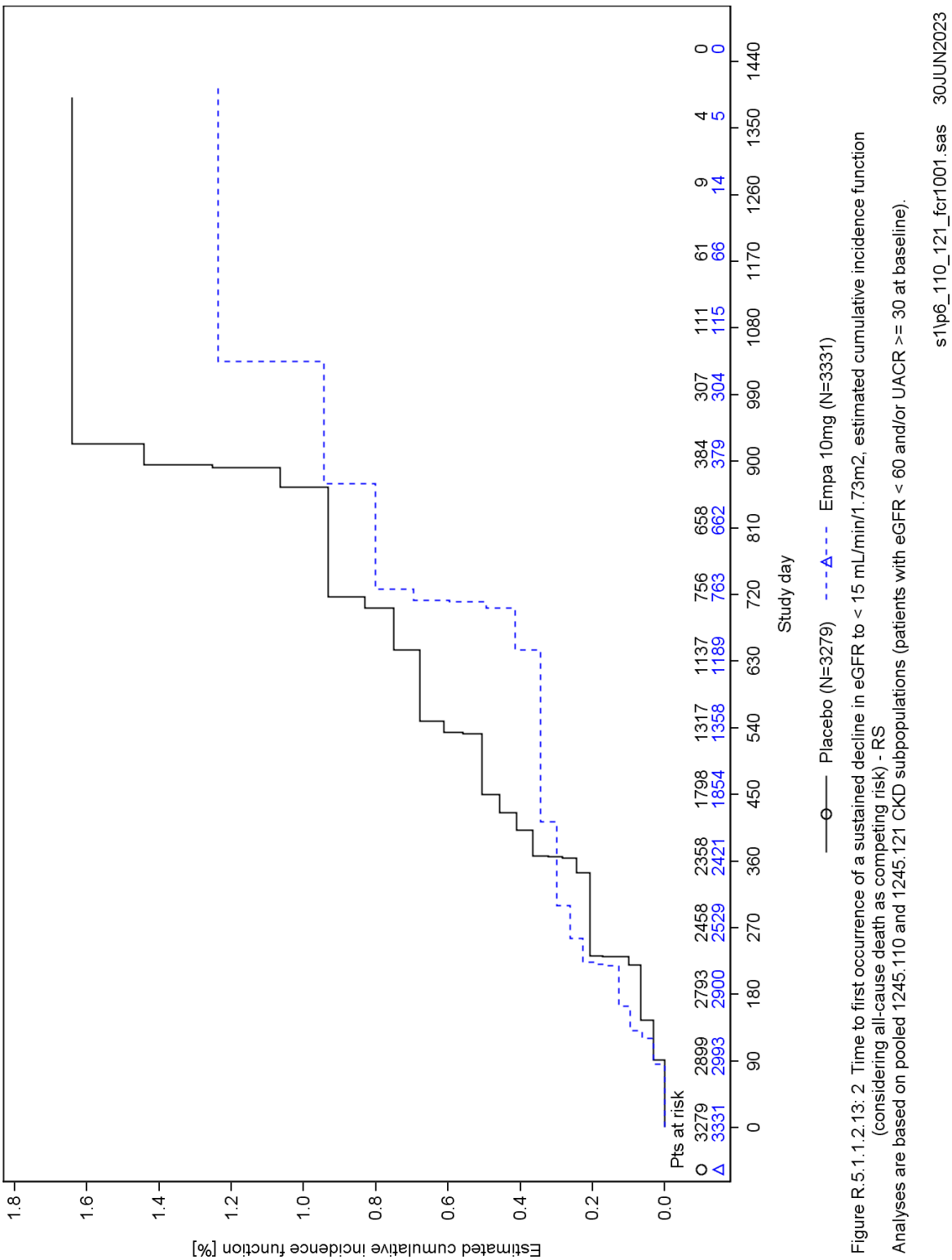


Figure R.5.1.1.2.13: 2 Time to first occurrence of a sustained decline in eGFR to < 15 mL/min/1.73m2, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**R.5.1.1.2.14**

R.5.1.1.2.14 Time to first occurrence of acute kidney injury

**Figure R.5.1.1.2.14: 1**

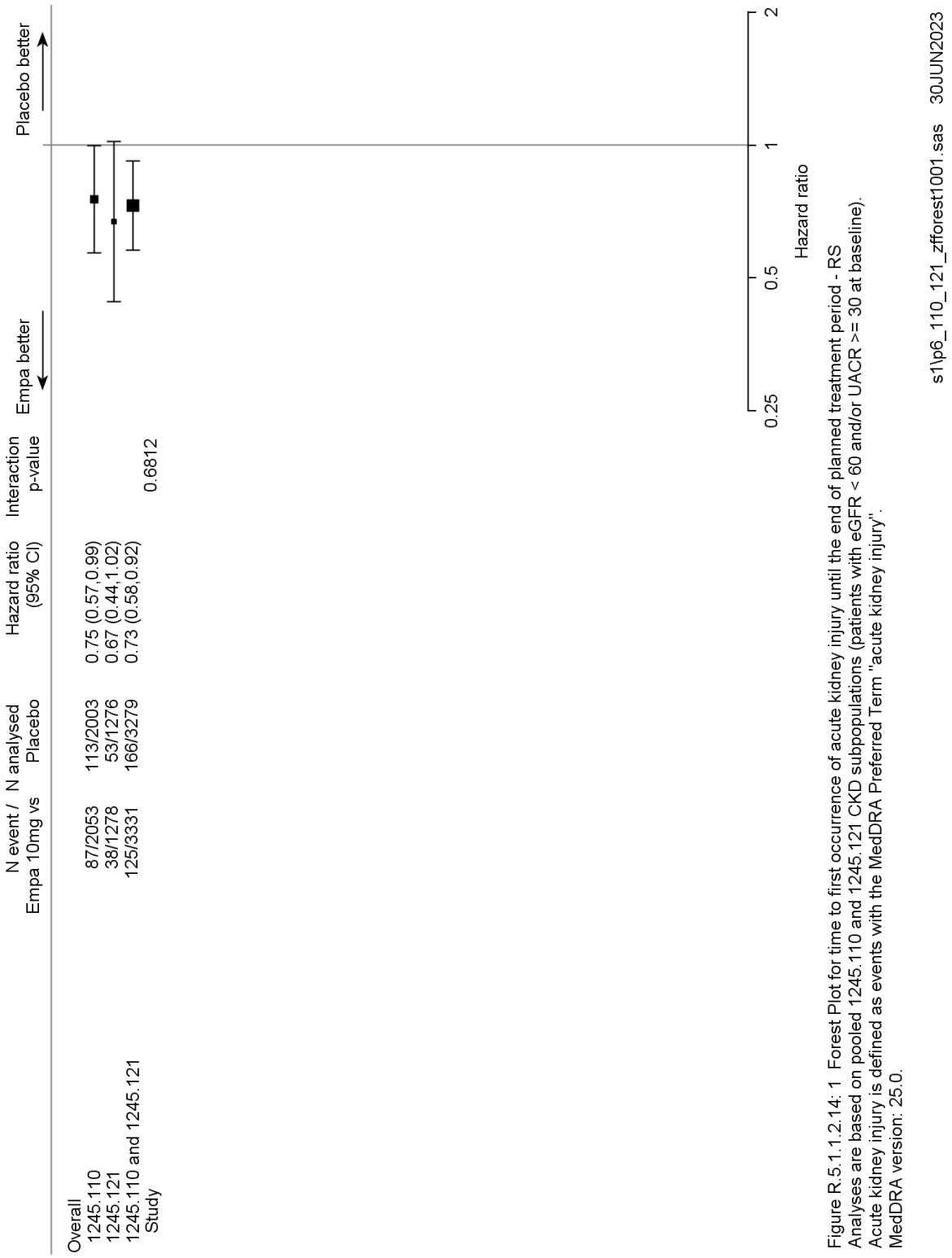


Figure R.5.1.1.2.14: 1 Forest Plot for time to first occurrence of acute kidney injury until the end of planned treatment period - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

Table R.5.1.1.2.14: 1 Cox Regression for time to first occurrence of acute kidney injury until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 166 | 5.1 | 2.91 | 3331 | 125 | 3.8 | 2.14 | 0.73 | (0.58,0.92) | 0.0072 | |
| Study | | | | | | | | | | | | 0.6812 |
| Sex | | | | | | | | | | | | 0.3135 |
| Male | 2024 | 105 | 5.2 | 3.10 | 2069 | 74 | 3.6 | 2.11 | 0.66 | (0.49,0.89) | 0.0065 | |
| Female | 1255 | 61 | 4.9 | 2.63 | 1262 | 51 | 4.0 | 2.17 | 0.85 | (0.58,1.23) | 0.3760 | |
| Age [years] | | | | | | | | | | | | 0.3476 |
| <65 | 767 | 31 | 4.0 | 2.49 | 705 | 26 | 3.7 | 2.27 | 0.91 | (0.54,1.53) | 0.7248 | |
| >=65 | 2512 | 135 | 5.4 | 3.02 | 2626 | 99 | 3.8 | 2.10 | 0.69 | (0.53,0.89) | 0.0049 | |
| Region | | | | | | | | | | | | 0.6085 |
| North America | 434 | 60 | 13.8 | 8.01 | 433 | 55 | 12.7 | 7.03 | 0.87 | (0.60,1.25) | 0.4452 | |
| Latin America | 931 | 37 | 4.0 | 2.49 | 944 | 26 | 2.8 | 1.73 | 0.69 | (0.42,1.14) | 0.1512 | |
| Europe | 1338 | 49 | 3.7 | 2.00 | 1361 | 29 | 2.1 | 1.16 | 0.57 | (0.36,0.90) | 0.0167 | |
| Asia | 405 | 9 | 2.2 | 1.24 | 413 | 5 | 1.2 | 0.66 | 0.52 | (0.18,1.56) | 0.2460 | |
| Other | 171 | 11 | 6.4 | 3.60 | 180 | 10 | 5.6 | 3.26 | 0.95 | (0.40,2.23) | 0.9008 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9263 |
| Diabetic | 1742 | 102 | 5.9 | 3.38 | 1780 | 78 | 4.4 | 2.52 | 0.73 | (0.55,0.99) | 0.0401 | |
| Non-Diabetic | 1537 | 64 | 4.2 | 2.37 | 1551 | 47 | 3.0 | 1.70 | 0.72 | (0.49,1.05) | 0.0844 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2237 |
| <30 | 1977 | 86 | 4.4 | 2.59 | 1930 | 53 | 2.7 | 1.61 | 0.62 | (0.44,0.87) | 0.0062 | |
| >=30 | 1302 | 80 | 6.1 | 3.35 | 1401 | 72 | 5.1 | 2.82 | 0.83 | (0.60,1.14) | 0.2493 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.9274 |
| <130 | 1686 | 95 | 5.6 | 3.47 | 1687 | 73 | 4.3 | 2.61 | 0.73 | (0.54,0.99) | 0.0463 | |
| >=130 | 1593 | 71 | 4.5 | 2.39 | 1644 | 52 | 3.2 | 1.70 | 0.72 | (0.50,1.03) | 0.0684 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.3018 |
| <75 | 1656 | 103 | 6.2 | 3.66 | 1613 | 81 | 5.0 | 2.94 | 0.78 | (0.58,1.04) | 0.0927 | |
| 75 to <85 | 1006 | 39 | 3.9 | 2.16 | 1085 | 33 | 3.0 | 1.71 | 0.80 | (0.50,1.27) | 0.3381 | |
| >=85 | 617 | 24 | 3.9 | 2.19 | 633 | 11 | 1.7 | 0.94 | 0.43 | (0.21,0.88) | 0.0212 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

Table R.5.1.1.2.14: 1 Cox Regression for time to first occurrence of acute kidney injury until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1289 |
| <30 | 251 | 22 | 8.8 | 5.70 | 263 | 29 | 11.0 | 6.78 | 1.21 | (0.69,2.11) | 0.5006 | |
| 30 to <45 | 899 | 61 | 6.8 | 3.89 | 909 | 42 | 4.6 | 2.66 | 0.70 | (0.47,1.04) | 0.0766 | |
| >=45 | 2128 | 83 | 3.9 | 2.21 | 2159 | 54 | 2.5 | 1.40 | 0.62 | (0.44,0.87) | 0.0061 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.1751 |
| Normal (<30) | 1218 | 50 | 4.1 | 2.31 | 1243 | 43 | 3.5 | 1.92 | 0.89 | (0.59,1.34) | 0.5888 | |
| Microalbuminuria (30 to <=300) | 1549 | 86 | 5.6 | 3.23 | 1547 | 55 | 3.6 | 2.03 | 0.58 | (0.41,0.82) | 0.0018 | |
| Macroalbuminuria (>300) | 500 | 28 | 5.6 | 3.24 | 525 | 27 | 5.1 | 3.07 | 0.93 | (0.55,1.59) | 0.8028 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3852 |
| Low, moderate or high | 2432 | 98 | 4.0 | 2.29 | 2496 | 69 | 2.8 | 1.55 | 0.68 | (0.50,0.92) | 0.0131 | |
| Very high | 836 | 66 | 7.9 | 4.67 | 820 | 56 | 6.8 | 4.08 | 0.83 | (0.58,1.19) | 0.3186 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.8785 |
| No | 573 | 31 | 5.4 | 3.00 | 579 | 24 | 4.1 | 2.24 | 0.75 | (0.44,1.29) | 0.3002 | |
| Yes | 2706 | 135 | 5.0 | 2.89 | 2752 | 101 | 3.7 | 2.11 | 0.72 | (0.56,0.93) | 0.0127 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3760 |
| No | 344 | 25 | 7.3 | 3.96 | 349 | 14 | 4.0 | 2.26 | 0.55 | (0.29,1.06) | 0.0758 | |
| Yes | 2935 | 141 | 4.8 | 2.78 | 2982 | 111 | 3.7 | 2.12 | 0.76 | (0.59,0.97) | 0.0292 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.1273 |
| No | 275 | 13 | 4.7 | 2.41 | 307 | 5 | 1.6 | 0.86 | 0.34 | (0.12,0.94) | 0.0379 | |
| Yes | 3004 | 153 | 5.1 | 2.96 | 3024 | 120 | 4.0 | 2.28 | 0.76 | (0.60,0.97) | 0.0277 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

**Figure R.5.1.1.2.14: 2**

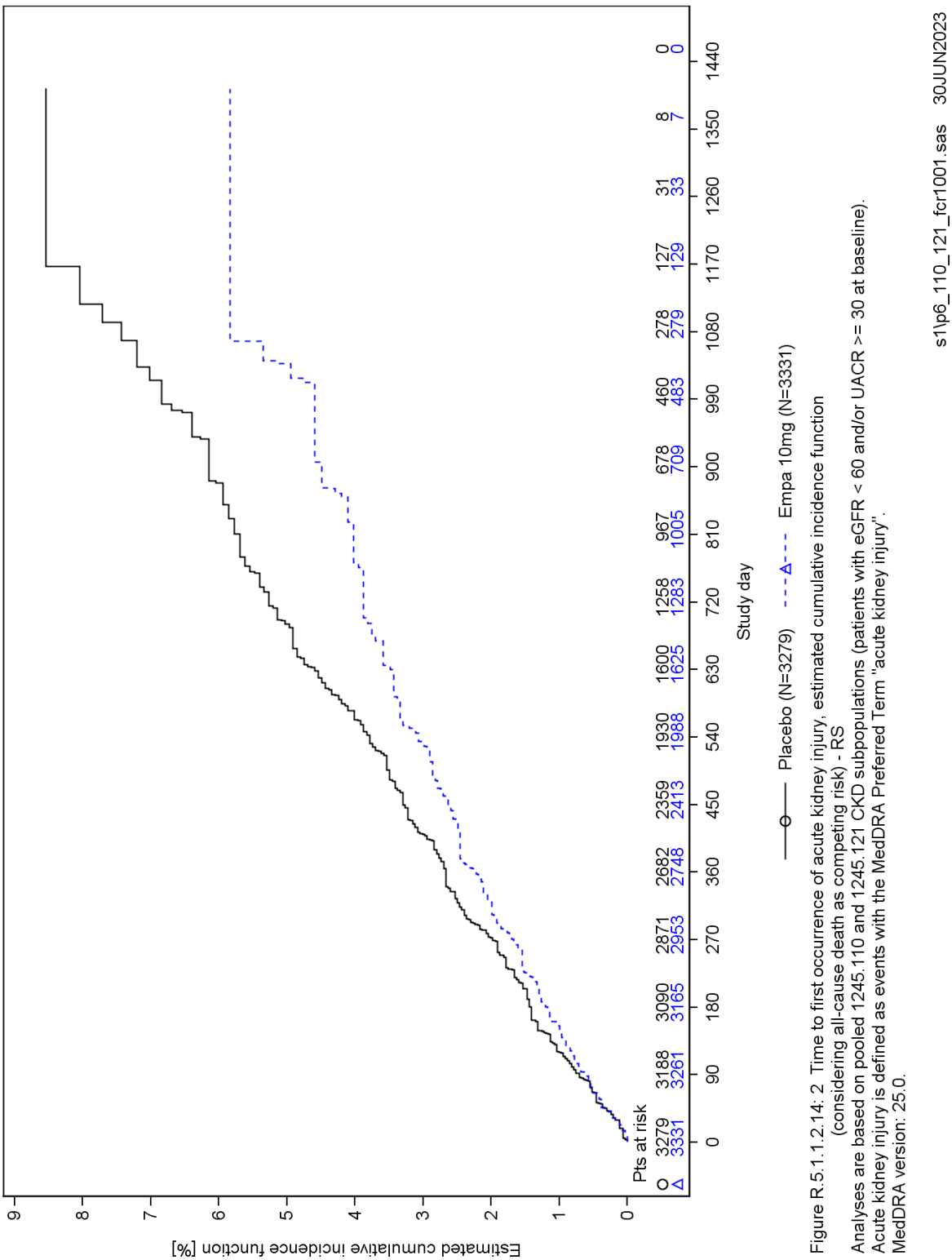


Figure R.5.1.1.2.14: 2 Time to first occurrence of acute kidney injury, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Acute kidney injury is defined as events with the MedDRA Preferred Term "acute kidney injury".
MedDRA version: 25.0.

**R.5.1.1.3**

R.5.1.1.3.1 Time to first occurrence of an adjudicated major cardiovascular event

**Figure R.5.1.1.3.1: 1**

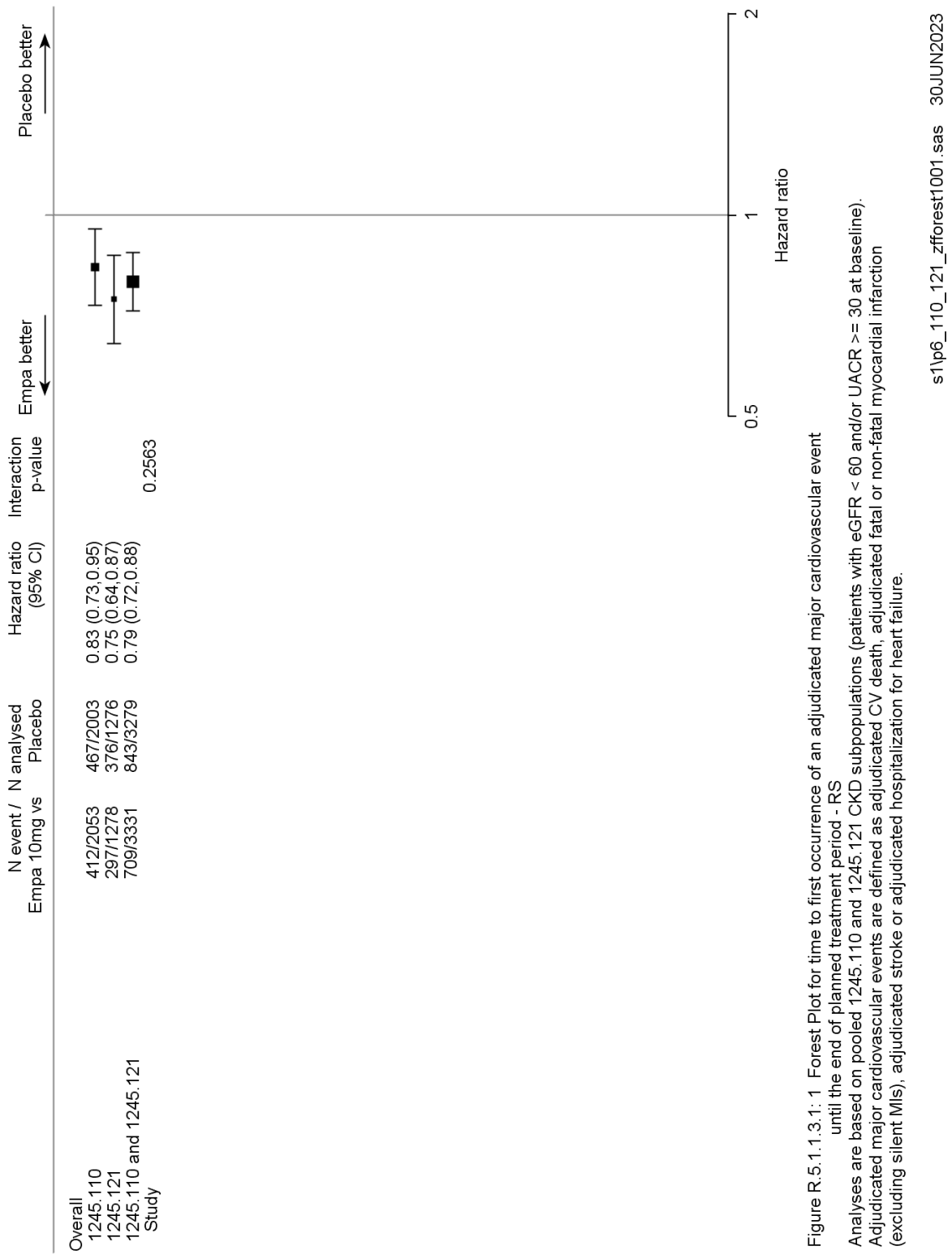


Figure R.5.1.1.3.1: 1 Forest Plot for time to first occurrence of an adjudicated major cardiovascular event until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.

Table R.5.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 843 | 25.7 | 16.23 | 3331 | 709 | 21.3 | 12.92 | 0.79 | (0.72,0.88) | <0.0001 | |
| Study | | | | | | | | | | | | 0.2563 |
| Sex | | | | | | | | | | | | 0.4800 |
| Male | 2024 | 553 | 27.3 | 18.15 | 2069 | 485 | 23.4 | 14.92 | 0.81 | (0.72,0.92) | 0.0010 | |
| Female | 1255 | 290 | 23.1 | 13.51 | 1262 | 224 | 17.7 | 10.02 | 0.75 | (0.63,0.90) | 0.0015 | |
| Age [years] | | | | | | | | | | | | 0.7022 |
| <65 | 767 | 208 | 27.1 | 18.83 | 705 | 154 | 21.8 | 14.47 | 0.77 | (0.62,0.94) | 0.0127 | |
| >=65 | 2512 | 635 | 25.3 | 15.53 | 2626 | 555 | 21.1 | 12.55 | 0.80 | (0.72,0.90) | 0.0002 | |
| Region | | | | | | | | | | | | 0.5211 |
| North America | 434 | 139 | 32.0 | 20.53 | 433 | 115 | 26.6 | 15.67 | 0.75 | (0.58,0.96) | 0.0216 | |
| Latin America | 931 | 227 | 24.4 | 16.48 | 944 | 207 | 21.9 | 14.63 | 0.88 | (0.73,1.07) | 0.1977 | |
| Europe | 1338 | 305 | 22.8 | 13.62 | 1361 | 255 | 18.7 | 10.86 | 0.80 | (0.68,0.95) | 0.0098 | |
| Asia | 405 | 125 | 30.9 | 20.11 | 413 | 93 | 22.5 | 13.33 | 0.66 | (0.51,0.87) | 0.0026 | |
| Other | 171 | 47 | 27.5 | 16.91 | 180 | 39 | 21.7 | 13.38 | 0.81 | (0.53,1.24) | 0.3272 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.5134 |
| Diabetic | 1742 | 500 | 28.7 | 18.61 | 1780 | 412 | 23.1 | 14.35 | 0.77 | (0.68,0.88) | 0.0001 | |
| Non-Diabetic | 1537 | 343 | 22.3 | 13.69 | 1551 | 297 | 19.1 | 11.35 | 0.83 | (0.71,0.97) | 0.0163 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1522 |
| <30 | 1977 | 533 | 27.0 | 17.74 | 1930 | 403 | 20.9 | 13.02 | 0.75 | (0.66,0.85) | <0.0001 | |
| >=30 | 1302 | 310 | 23.8 | 14.17 | 1401 | 306 | 21.8 | 12.80 | 0.87 | (0.74,1.02) | 0.0803 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.6337 |
| <130 | 1686 | 463 | 27.5 | 18.85 | 1687 | 382 | 22.6 | 14.65 | 0.78 | (0.68,0.89) | 0.0003 | |
| >=130 | 1593 | 380 | 23.9 | 13.89 | 1644 | 327 | 19.9 | 11.36 | 0.82 | (0.70,0.95) | 0.0068 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.2062 |
| <75 | 1656 | 445 | 26.9 | 17.38 | 1613 | 384 | 23.8 | 14.90 | 0.86 | (0.75,0.99) | 0.0329 | |
| 75 to <85 | 1006 | 259 | 25.7 | 15.83 | 1085 | 207 | 19.1 | 11.36 | 0.70 | (0.58,0.84) | 0.0001 | |
| >=85 | 617 | 139 | 22.5 | 13.94 | 633 | 118 | 18.6 | 10.86 | 0.78 | (0.61,0.99) | 0.0433 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.

Table R.5.1.1.3.1: 1 Cox Regression for time to first occurrence of an adjudicated major cardiovascular event until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.3145 |
| <30 | 251 | 93 | 37.1 | 27.54 | 263 | 88 | 33.5 | 22.71 | 0.77 | (0.58,1.04) | 0.0859 | |
| 30 to <45 | 899 | 240 | 26.7 | 16.91 | 909 | 218 | 24.0 | 14.80 | 0.89 | (0.74,1.07) | 0.2077 | |
| >=45 | 2128 | 510 | 24.0 | 14.85 | 2159 | 403 | 18.7 | 11.12 | 0.75 | (0.66,0.85) | <0.0001 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8689 |
| Normal (<30) | 1218 | 234 | 19.2 | 11.61 | 1243 | 203 | 16.3 | 9.42 | 0.82 | (0.68,0.99) | 0.0394 | |
| Microalbuminuria (30 to <=300) | 1549 | 422 | 27.2 | 17.36 | 1547 | 338 | 21.8 | 13.42 | 0.78 | (0.67,0.89) | 0.0005 | |
| Macroalbuminuria (>300) | 500 | 182 | 36.4 | 24.88 | 525 | 167 | 31.8 | 21.25 | 0.82 | (0.66,1.01) | 0.0580 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.1326 |
| Low, moderate or high | 2432 | 558 | 22.9 | 14.20 | 2496 | 453 | 18.1 | 10.74 | 0.76 | (0.67,0.86) | <0.0001 | |
| Very high | 836 | 280 | 33.5 | 22.43 | 820 | 256 | 31.2 | 20.59 | 0.89 | (0.75,1.06) | 0.1925 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.4938 |
| No | 573 | 162 | 28.3 | 17.31 | 579 | 145 | 25.0 | 14.85 | 0.85 | (0.68,1.07) | 0.1616 | |
| Yes | 2706 | 681 | 25.2 | 16.00 | 2752 | 564 | 20.5 | 12.51 | 0.78 | (0.70,0.87) | <0.0001 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3080 |
| No | 344 | 88 | 25.6 | 14.97 | 349 | 80 | 22.9 | 13.51 | 0.92 | (0.68,1.25) | 0.6010 | |
| Yes | 2935 | 755 | 25.7 | 16.40 | 2982 | 629 | 21.1 | 12.85 | 0.78 | (0.70,0.87) | <0.0001 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.2920 |
| No | 275 | 54 | 19.6 | 10.49 | 307 | 37 | 12.1 | 6.56 | 0.64 | (0.42,0.97) | 0.0356 | |
| Yes | 3004 | 789 | 26.3 | 16.87 | 3024 | 672 | 22.2 | 13.65 | 0.80 | (0.73,0.89) | <0.0001 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.

**Figure R.5.1.1.3.1: 2**

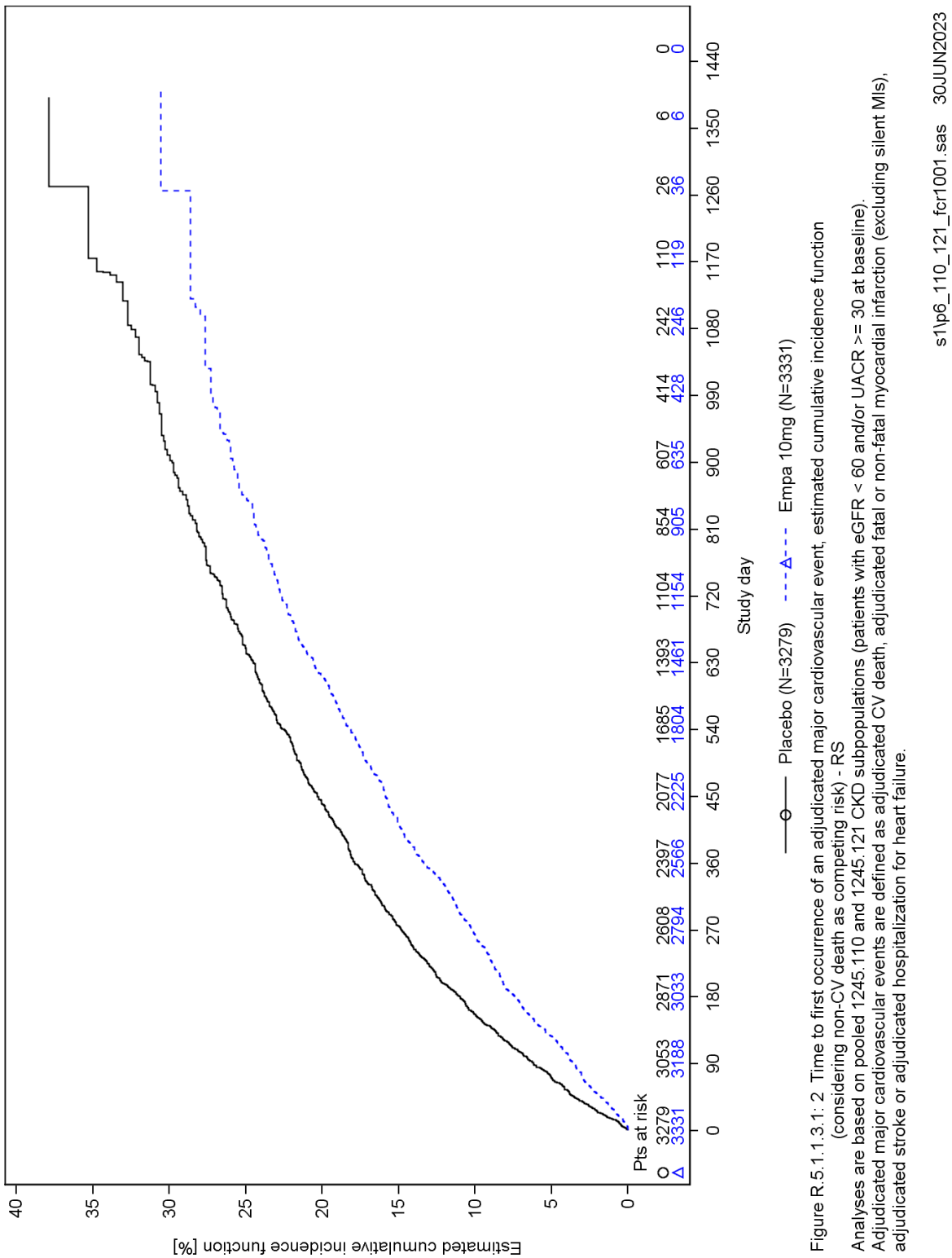


Figure R.5.1.1.3.1: 2 Time to first occurrence of an adjudicated major cardiovascular event, estimated cumulative incidence function (considering non-CV death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Adjudicated major cardiovascular events are defined as adjudicated CV death, adjudicated fatal or non-fatal myocardial infarction (excluding silent MIs), adjudicated stroke or adjudicated hospitalization for heart failure.

R.5.1.1.3.2 Time to first occurrence of an adjudicated myocardial infarction

**Figure R.5.1.1.3.2: 1**

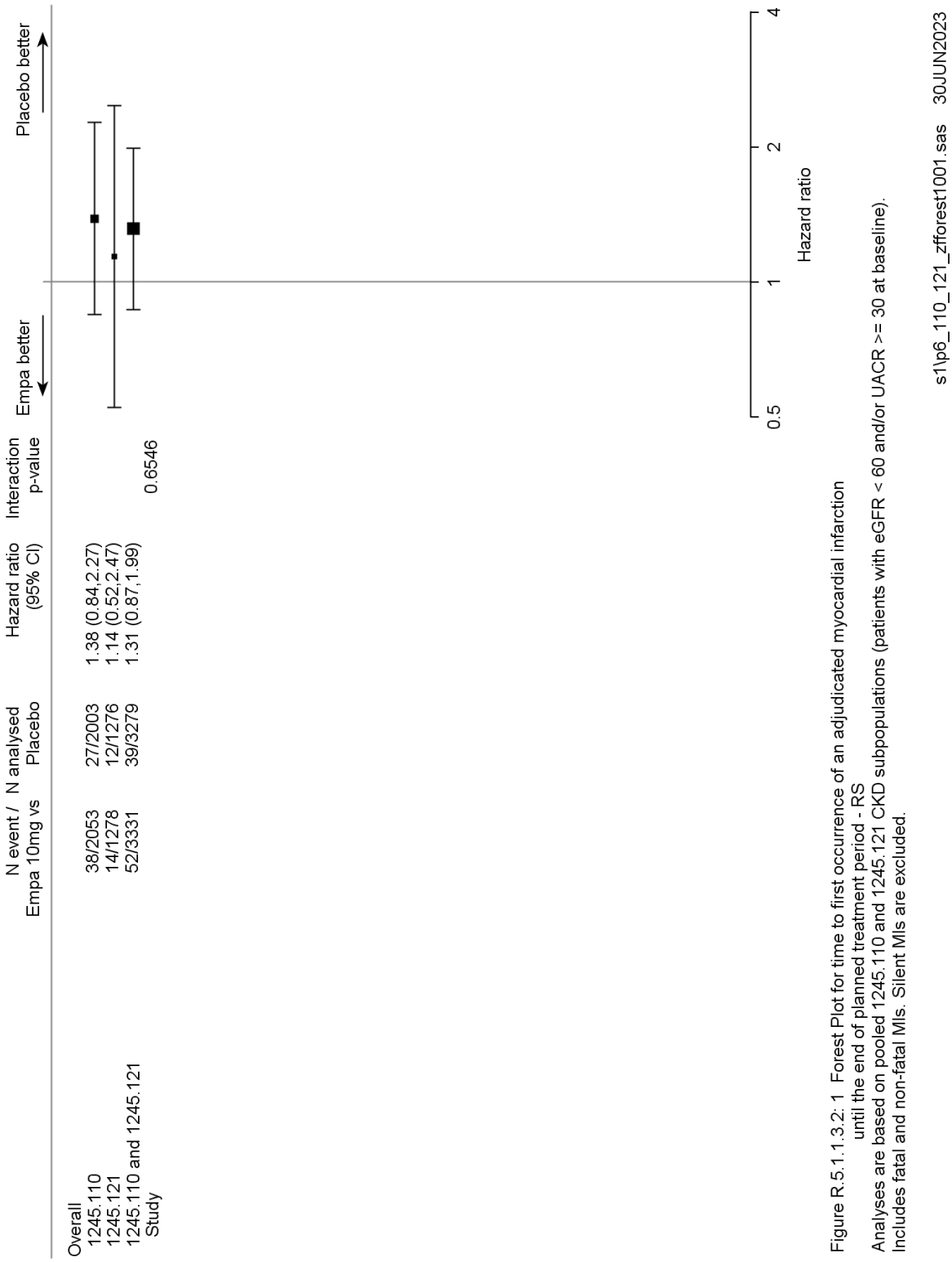


Figure R.5.1.1.3.2: 1 Forest Plot for time to first occurrence of an adjudicated myocardial infarction until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

Table R.5.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 39 | 1.2 | 0.67 | 3331 | 52 | 1.6 | 0.88 | 1.31 | (0.87, 1.99) | 0.2007 | |
| Study | | | | | | | | | | | | 0.6546 |
| Sex | | | | | | | | | | | | 0.8238 |
| Male | 2024 | 22 | 1.1 | 0.64 | 2069 | 29 | 1.4 | 0.82 | 1.26 | (0.72, 2.19) | 0.4174 | |
| Female | 1255 | 17 | 1.4 | 0.72 | 1262 | 23 | 1.8 | 0.97 | 1.38 | (0.74, 2.59) | 0.3109 | |
| Age [years] | | | | | | | | | | | | 0.8877 |
| <65 | 767 | 7 | 0.9 | 0.56 | 705 | 8 | 1.1 | 0.69 | 1.23 | (0.45, 3.40) | 0.6880 | |
| >=65 | 2512 | 32 | 1.3 | 0.71 | 2626 | 44 | 1.7 | 0.93 | 1.33 | (0.85, 2.10) | 0.2153 | |
| Region | | | | | | | | | | | | 0.1016 |
| North America | 434 | 16 | 3.7 | 2.01 | 433 | 15 | 3.5 | 1.85 | 0.90 | (0.44, 1.82) | 0.7701 | |
| Latin America | 931 | 2 | 0.2 | 0.13 | 944 | 15 | 1.6 | 1.00 | 7.53 | (1.72,32.95) | 0.0073 | |
| Europe | 1338 | 14 | 1.0 | 0.57 | 1361 | 19 | 1.4 | 0.76 | 1.36 | (0.68, 2.72) | 0.3800 | |
| Asia | 405 | 5 | 1.2 | 0.69 | 413 | 3 | 0.7 | 0.39 | 0.57 | (0.14, 2.39) | 0.4424 | |
| Other | 171 | 2 | 1.2 | 0.65 | 180 | 0 | 0 | 0.00 | <0.01 | | 0.9790 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1430 |
| Diabetic | 1742 | 27 | 1.5 | 0.88 | 1780 | 28 | 1.6 | 0.90 | 1.02 | (0.60, 1.73) | 0.9386 | |
| Non-Diabetic | 1537 | 12 | 0.8 | 0.44 | 1551 | 24 | 1.5 | 0.86 | 1.96 | (0.98, 3.92) | 0.0573 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0649 |
| <30 | 1977 | 28 | 1.4 | 0.84 | 1930 | 26 | 1.3 | 0.78 | 0.96 | (0.56, 1.64) | 0.8746 | |
| >=30 | 1302 | 11 | 0.8 | 0.45 | 1401 | 26 | 1.9 | 1.01 | 2.21 | (1.09, 4.47) | 0.0279 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5960 |
| <130 | 1686 | 17 | 1.0 | 0.61 | 1687 | 21 | 1.2 | 0.74 | 1.16 | (0.61, 2.20) | 0.6522 | |
| >=130 | 1593 | 22 | 1.4 | 0.73 | 1644 | 31 | 1.9 | 1.01 | 1.46 | (0.84, 2.52) | 0.1786 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.0303 |
| <75 | 1656 | 20 | 1.2 | 0.70 | 1613 | 34 | 2.1 | 1.22 | 1.72 | (0.99, 2.99) | 0.0541 | |
| 75 to <85 | 1006 | 19 | 1.9 | 1.05 | 1085 | 10 | 0.9 | 0.51 | 0.48 | (0.22, 1.04) | 0.0614 | |
| >=85 | 617 | 0 | 0 | 0.00 | 633 | 8 | 1.3 | 0.69 | >999.99 | | 0.9720 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

Table R.5.1.1.3.2: 1 Cox Regression for time to first occurrence of an adjudicated myocardial infarction until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6322 |
| <30 | 251 | 5 | 2.0 | 1.25 | 263 | 6 | 2.3 | 1.37 | 1.26 | (0.38, 4.14) | 0.7080 | |
| 30 to <45 | 899 | 10 | 1.1 | 0.63 | 909 | 18 | 2.0 | 1.12 | 1.79 | (0.83, 3.88) | 0.1400 | |
| >=45 | 2128 | 24 | 1.1 | 0.63 | 2159 | 28 | 1.3 | 0.73 | 1.13 | (0.65, 1.95) | 0.6639 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.6983 |
| Normal (<30) | 1218 | 12 | 1.0 | 0.55 | 1243 | 17 | 1.4 | 0.75 | 1.47 | (0.70, 3.07) | 0.3099 | |
| Microalbuminuria (30 to <=300) | 1549 | 18 | 1.2 | 0.66 | 1547 | 21 | 1.4 | 0.77 | 1.08 | (0.58, 2.04) | 0.8025 | |
| Macroalbuminuria (>300) | 500 | 9 | 1.8 | 1.02 | 525 | 14 | 2.7 | 1.59 | 1.65 | (0.71, 3.82) | 0.2442 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3638 |
| Low, moderate or high | 2432 | 27 | 1.1 | 0.62 | 2496 | 32 | 1.3 | 0.71 | 1.15 | (0.69, 1.92) | 0.5991 | |
| Very high | 836 | 12 | 1.4 | 0.83 | 820 | 20 | 2.4 | 1.44 | 1.73 | (0.84, 3.54) | 0.1356 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.8558 |
| No | 573 | 9 | 1.6 | 0.86 | 579 | 11 | 1.9 | 1.02 | 1.22 | (0.51, 2.95) | 0.6570 | |
| Yes | 2706 | 30 | 1.1 | 0.63 | 2752 | 41 | 1.5 | 0.85 | 1.34 | (0.84, 2.15) | 0.2239 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9519 |
| No | 344 | 4 | 1.2 | 0.62 | 349 | 5 | 1.4 | 0.79 | 1.26 | (0.34, 4.71) | 0.7291 | |
| Yes | 2935 | 35 | 1.2 | 0.68 | 2982 | 47 | 1.6 | 0.89 | 1.32 | (0.85, 2.04) | 0.2180 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.1984 |
| No | 275 | 6 | 2.2 | 1.11 | 307 | 4 | 1.3 | 0.68 | 0.60 | (0.17, 2.12) | 0.4266 | |
| Yes | 3004 | 33 | 1.1 | 0.63 | 3024 | 48 | 1.6 | 0.90 | 1.44 | (0.93, 2.25) | 0.1046 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

**Figure R.5.1.1.3.2: 2**

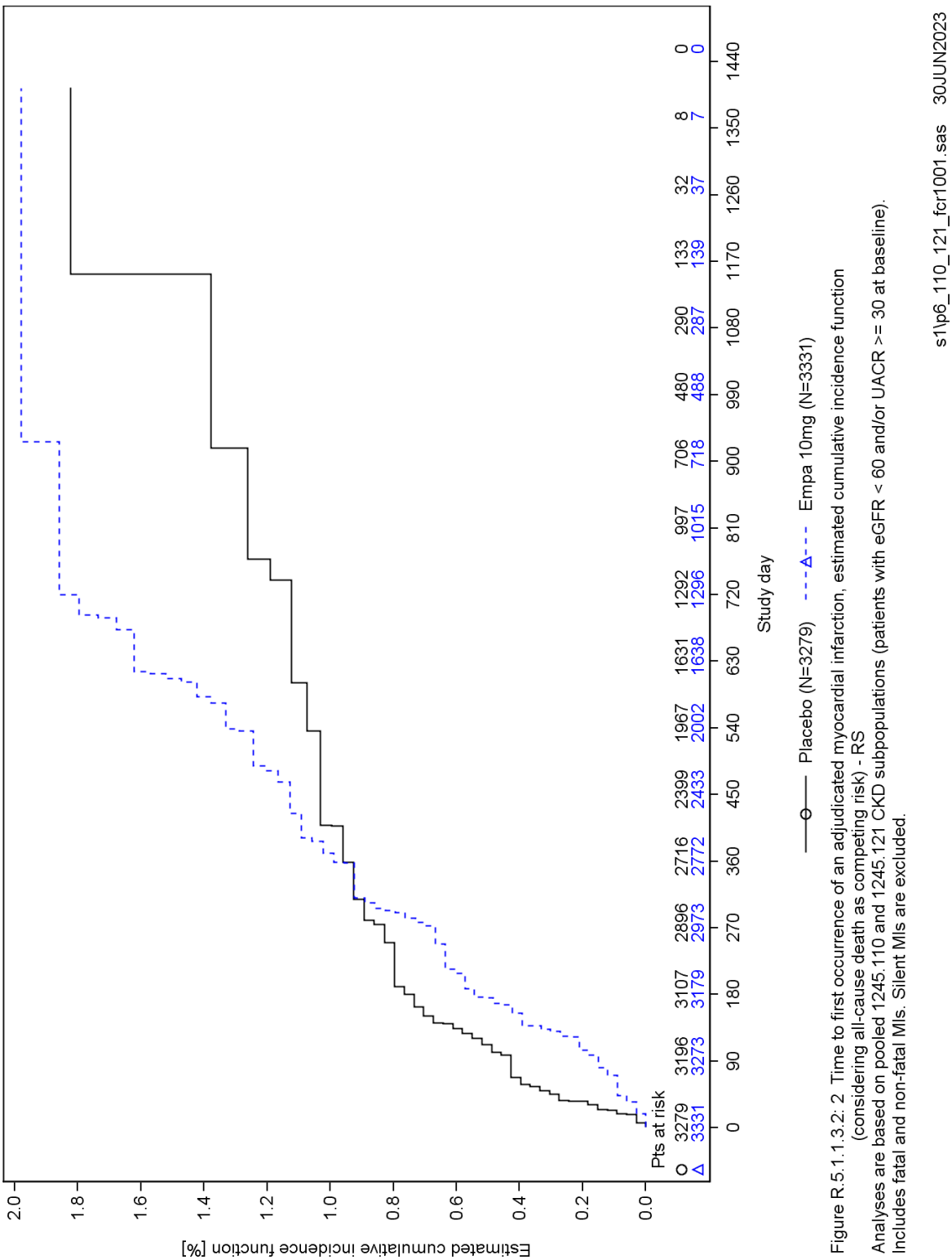


Figure R.5.1.1.3.2: 2 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

**Figure R.5.1.1.3.2: 3**

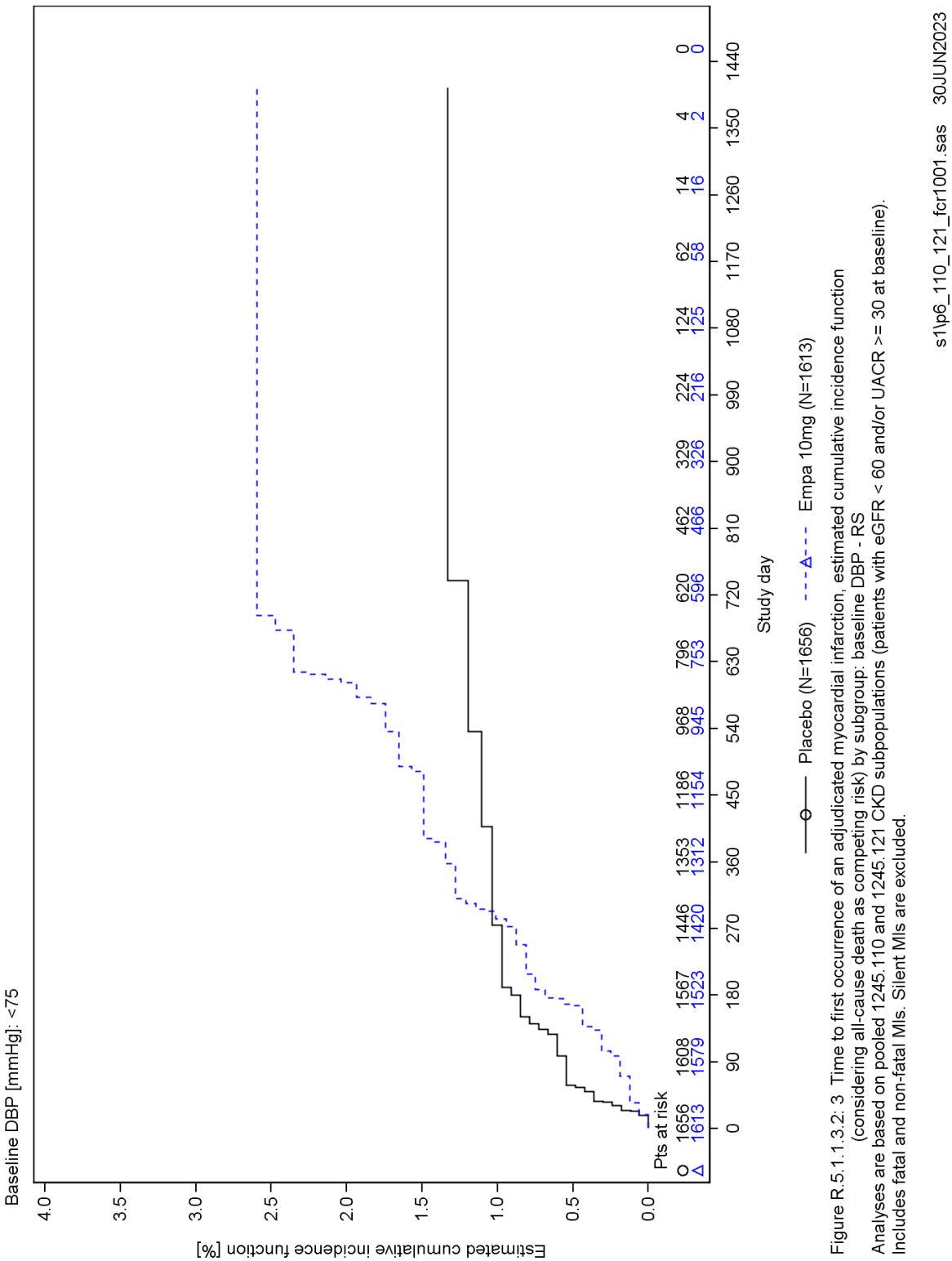


Figure R.5.1.1.3.2: 3 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline DBP - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

**Figure R.5.1.1.3.2: 3**

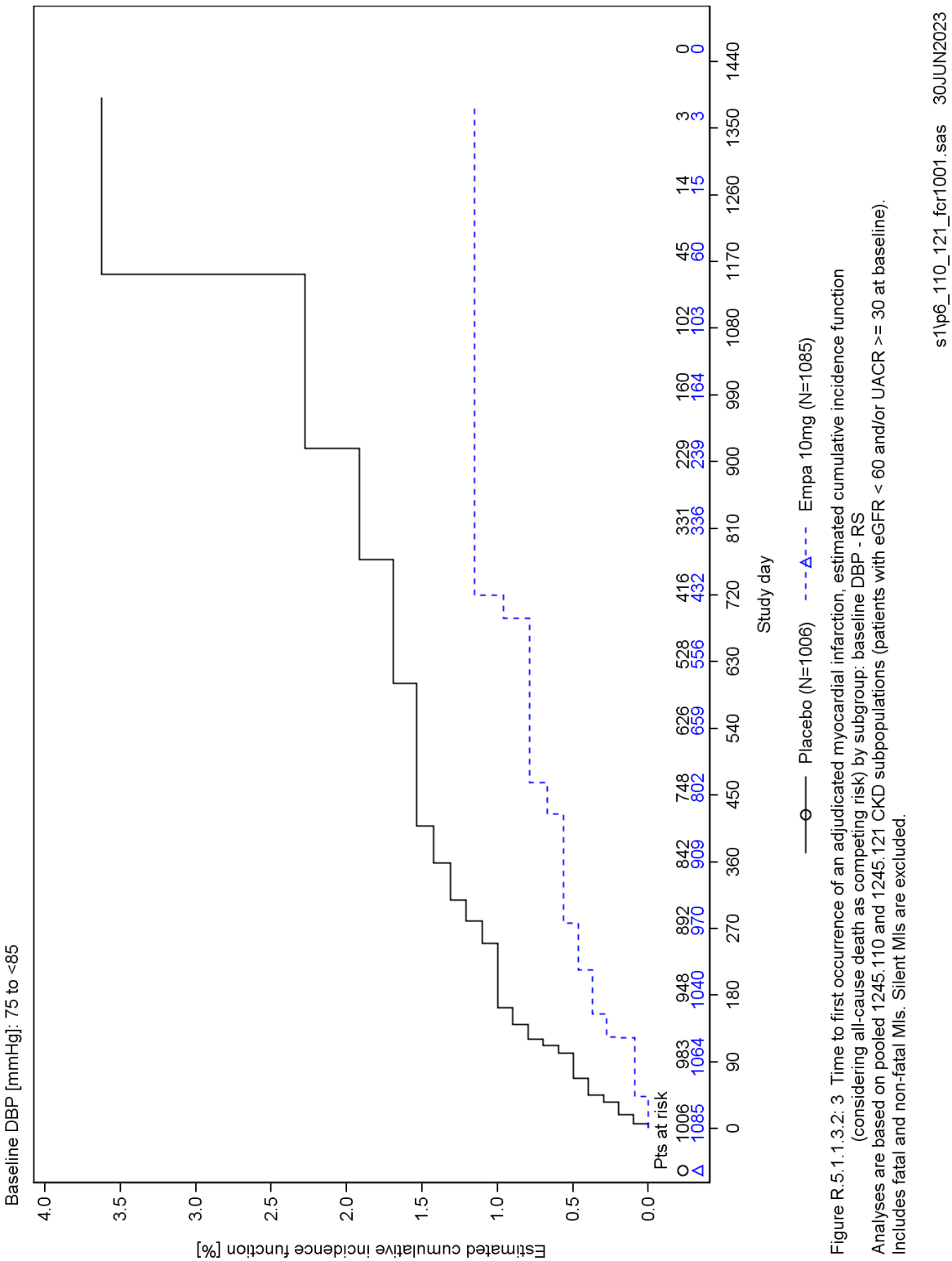


Figure R.5.1.1.3.2: 3 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline DBP - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

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**Figure R.5.1.1.3.2: 3**

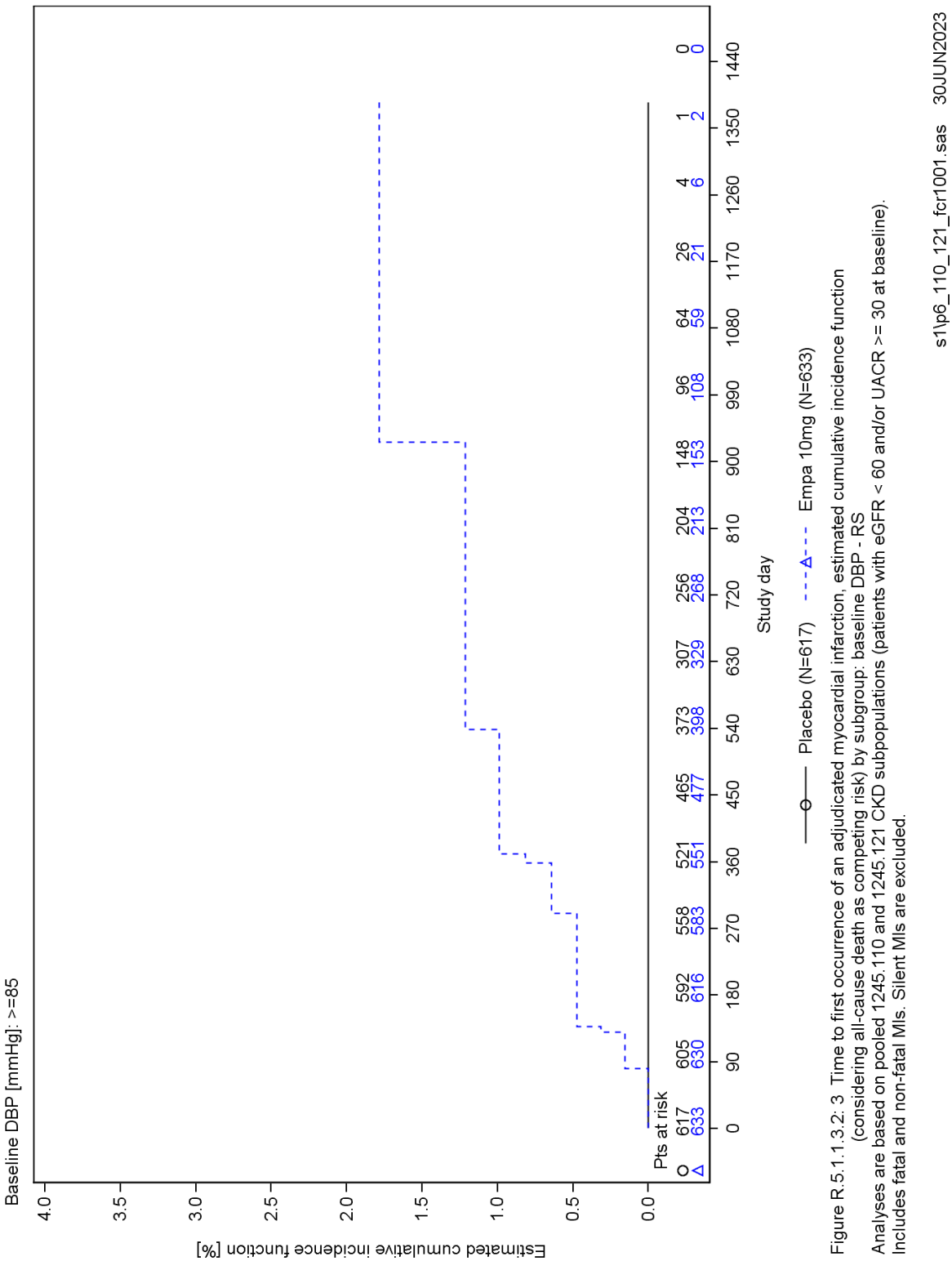


Figure R.5.1.1.3.2: 3 Time to first occurrence of an adjudicated myocardial infarction, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline DBP - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Includes fatal and non-fatal MIs. Silent MIs are excluded.

R.5.1.1.3.3 Time to first occurrence of an adjudicated stroke

**Figure R.5.1.1.3.3: 1**

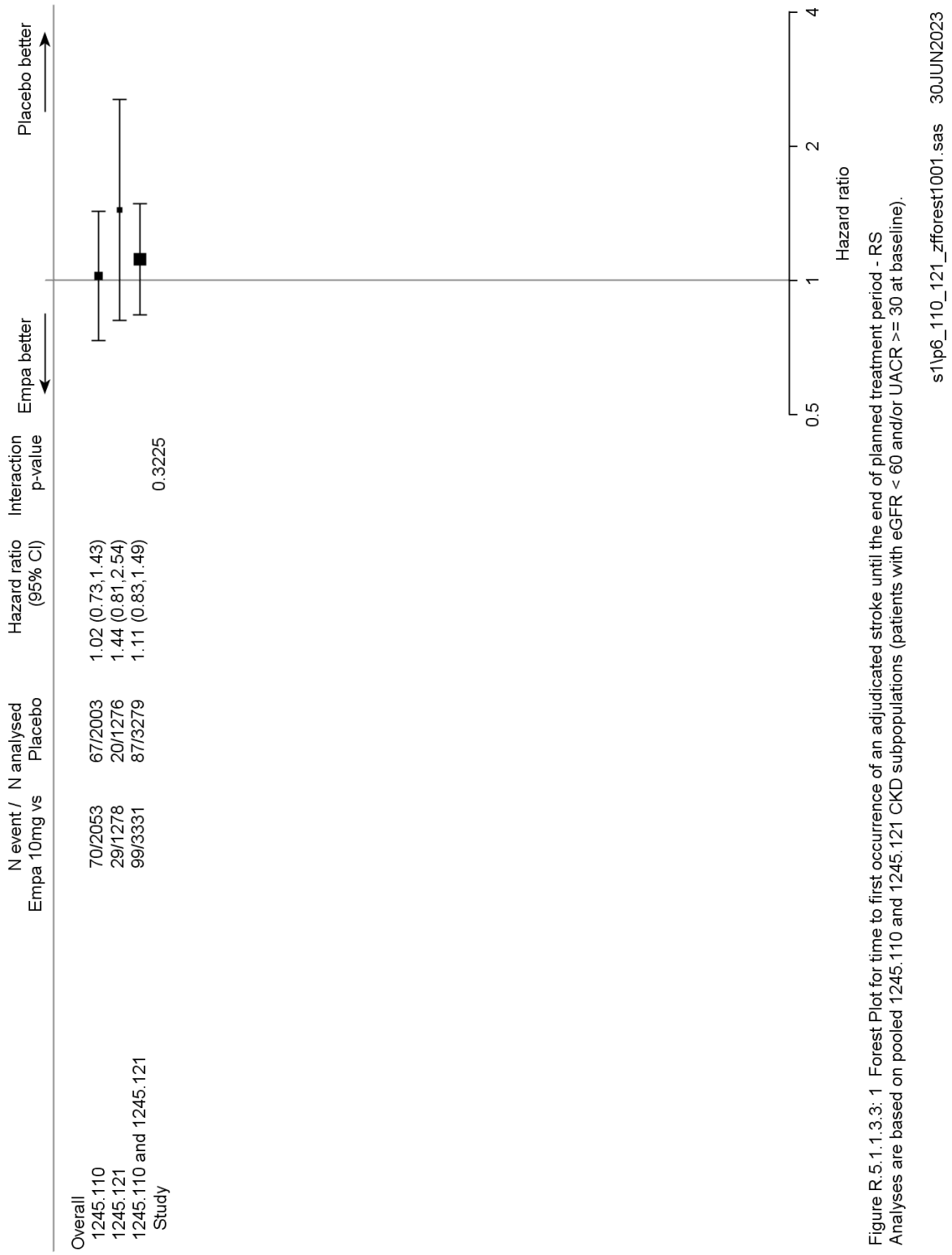


Figure R.5.1.1.3.3: 1 Forest Plot for time to first occurrence of an adjudicated stroke until the end of planned treatment period - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3279 | 87 | 2.7 | 1.51 | 3331 | 99 | 3.0 | 1.69 | 1.11 | (0.83,1.49) | 0.4636 | |
| Study | | | | | | | | | | | | 0.3225 |
| Sex | | | | | | | | | | | | 0.3479 |
| Male | 2024 | 49 | 2.4 | 1.43 | 2069 | 63 | 3.0 | 1.79 | 1.25 | (0.86,1.81) | 0.2468 | |
| Female | 1255 | 38 | 3.0 | 1.62 | 1262 | 36 | 2.9 | 1.53 | 0.94 | (0.60,1.48) | 0.7908 | |
| Age [years] | | | | | | | | | | | | 0.6284 |
| <65 | 767 | 16 | 2.1 | 1.28 | 705 | 14 | 2.0 | 1.21 | 0.94 | (0.46,1.93) | 0.8741 | |
| >=65 | 2512 | 71 | 2.8 | 1.57 | 2626 | 85 | 3.2 | 1.81 | 1.15 | (0.84,1.57) | 0.3994 | |
| Region | | | | | | | | | | | | 0.4258 |
| North America | 434 | 18 | 4.1 | 2.26 | 433 | 14 | 3.2 | 1.71 | 0.74 | (0.37,1.50) | 0.4084 | |
| Latin America | 931 | 25 | 2.7 | 1.68 | 944 | 29 | 3.1 | 1.94 | 1.16 | (0.68,1.98) | 0.5852 | |
| Europe | 1338 | 28 | 2.1 | 1.14 | 1361 | 32 | 2.4 | 1.28 | 1.12 | (0.68,1.86) | 0.6577 | |
| Asia | 405 | 11 | 2.7 | 1.52 | 413 | 21 | 5.1 | 2.80 | 1.83 | (0.88,3.80) | 0.1039 | |
| Other | 171 | 5 | 2.9 | 1.65 | 180 | 3 | 1.7 | 0.96 | 0.59 | (0.14,2.45) | 0.4643 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9282 |
| Diabetic | 1742 | 46 | 2.6 | 1.50 | 1780 | 53 | 3.0 | 1.70 | 1.13 | (0.76,1.68) | 0.5448 | |
| Non-Diabetic | 1537 | 41 | 2.7 | 1.52 | 1551 | 46 | 3.0 | 1.67 | 1.10 | (0.72,1.68) | 0.6564 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7073 |
| <30 | 1977 | 53 | 2.7 | 1.59 | 1930 | 56 | 2.9 | 1.70 | 1.06 | (0.73,1.55) | 0.7519 | |
| >=30 | 1302 | 34 | 2.6 | 1.40 | 1401 | 43 | 3.1 | 1.67 | 1.19 | (0.76,1.86) | 0.4511 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5156 |
| <130 | 1686 | 39 | 2.3 | 1.41 | 1687 | 50 | 3.0 | 1.79 | 1.23 | (0.81,1.87) | 0.3296 | |
| >=130 | 1593 | 48 | 3.0 | 1.60 | 1644 | 49 | 3.0 | 1.60 | 1.02 | (0.68,1.51) | 0.9353 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.8480 |
| <75 | 1656 | 48 | 2.9 | 1.69 | 1613 | 56 | 3.5 | 2.02 | 1.17 | (0.80,1.73) | 0.4151 | |
| 75 to <85 | 1006 | 26 | 2.6 | 1.43 | 1085 | 27 | 2.5 | 1.40 | 0.98 | (0.57,1.68) | 0.9371 | |
| >=85 | 617 | 13 | 2.1 | 1.18 | 633 | 16 | 2.5 | 1.38 | 1.20 | (0.58,2.49) | 0.6310 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.3.3: 1 Cox Regression for time to first occurrence of an adjudicated stroke until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.3105 |
| <30 | 251 | 4 | 1.6 | 1.00 | 263 | 8 | 3.0 | 1.81 | 1.95 | (0.59,6.50) | 0.2754 | |
| 30 to <45 | 899 | 31 | 3.4 | 1.95 | 909 | 26 | 2.9 | 1.62 | 0.83 | (0.49,1.39) | 0.4721 | |
| >=45 | 2128 | 52 | 2.4 | 1.38 | 2159 | 65 | 3.0 | 1.70 | 1.22 | (0.85,1.76) | 0.2846 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7246 |
| Normal (<30) | 1218 | 27 | 2.2 | 1.24 | 1243 | 30 | 2.4 | 1.34 | 1.09 | (0.65,1.83) | 0.7463 | |
| Microalbuminuria (30 to <=300) | 1549 | 45 | 2.9 | 1.67 | 1547 | 48 | 3.1 | 1.77 | 1.05 | (0.70,1.58) | 0.8106 | |
| Macroalbuminuria (>300) | 500 | 14 | 2.8 | 1.60 | 525 | 21 | 4.0 | 2.36 | 1.44 | (0.73,2.84) | 0.2873 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.6755 |
| Low, moderate or high | 2432 | 62 | 2.5 | 1.44 | 2496 | 70 | 2.8 | 1.58 | 1.09 | (0.77,1.53) | 0.6339 | |
| Very high | 836 | 24 | 2.9 | 1.66 | 820 | 29 | 3.5 | 2.07 | 1.25 | (0.72,2.14) | 0.4261 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.0421 |
| No | 573 | 9 | 1.6 | 0.85 | 579 | 21 | 3.6 | 1.97 | 2.33 | (1.07,5.09) | 0.0338 | |
| Yes | 2706 | 78 | 2.9 | 1.66 | 2752 | 78 | 2.8 | 1.63 | 0.97 | (0.71,1.33) | 0.8658 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.9166 |
| No | 344 | 9 | 2.6 | 1.40 | 349 | 9 | 2.6 | 1.43 | 1.06 | (0.42,2.68) | 0.9005 | |
| Yes | 2935 | 78 | 2.7 | 1.52 | 2982 | 90 | 3.0 | 1.72 | 1.12 | (0.83,1.51) | 0.4730 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.0387 |
| No | 275 | 18 | 6.5 | 3.36 | 307 | 10 | 3.3 | 1.73 | 0.52 | (0.24,1.14) | 0.1028 | |
| Yes | 3004 | 69 | 2.3 | 1.32 | 3024 | 89 | 2.9 | 1.68 | 1.27 | (0.93,1.74) | 0.1391 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.3: 2**

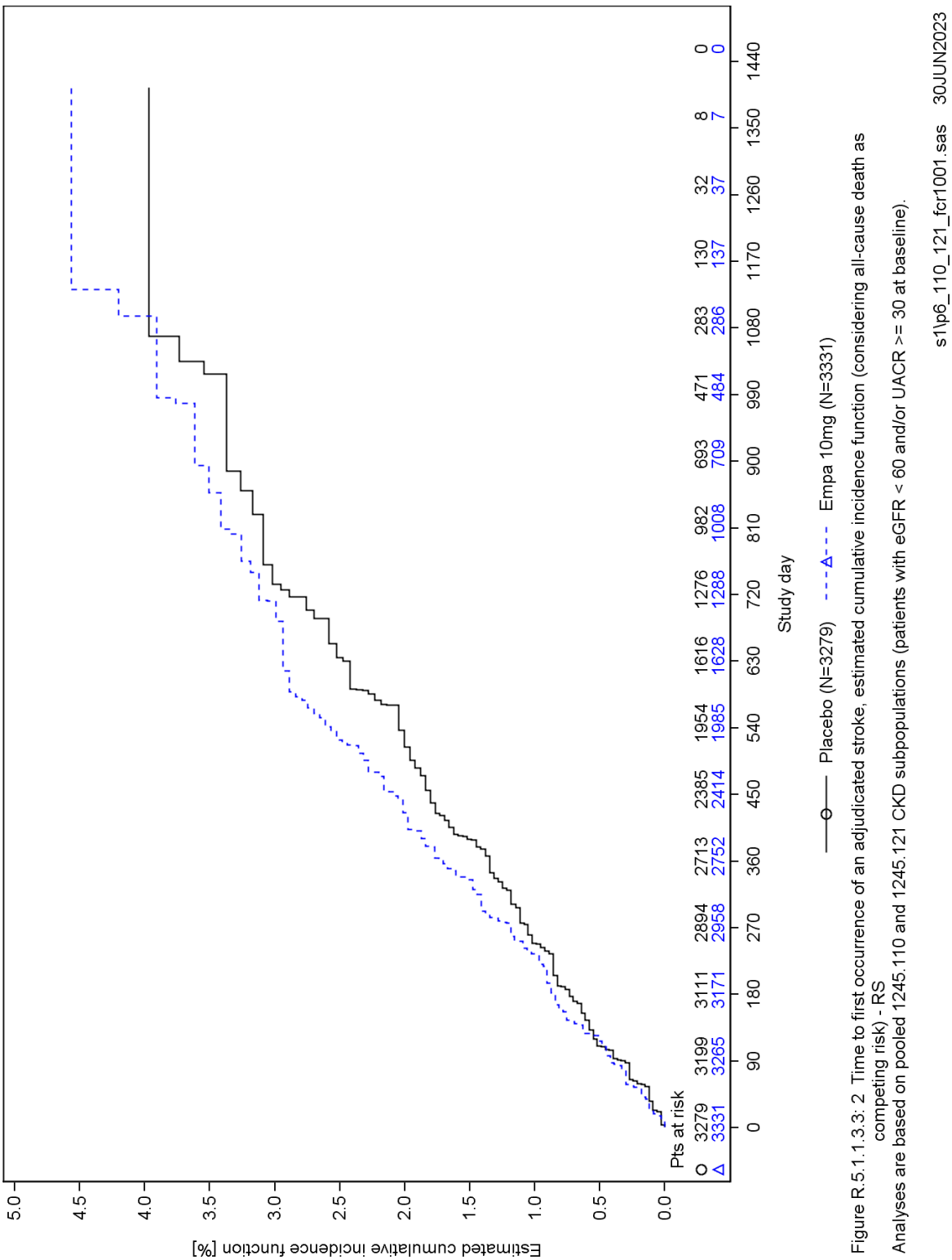


Figure R.5.1.1.3.3: 2 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**Figure R.5.1.1.3.3: 3**

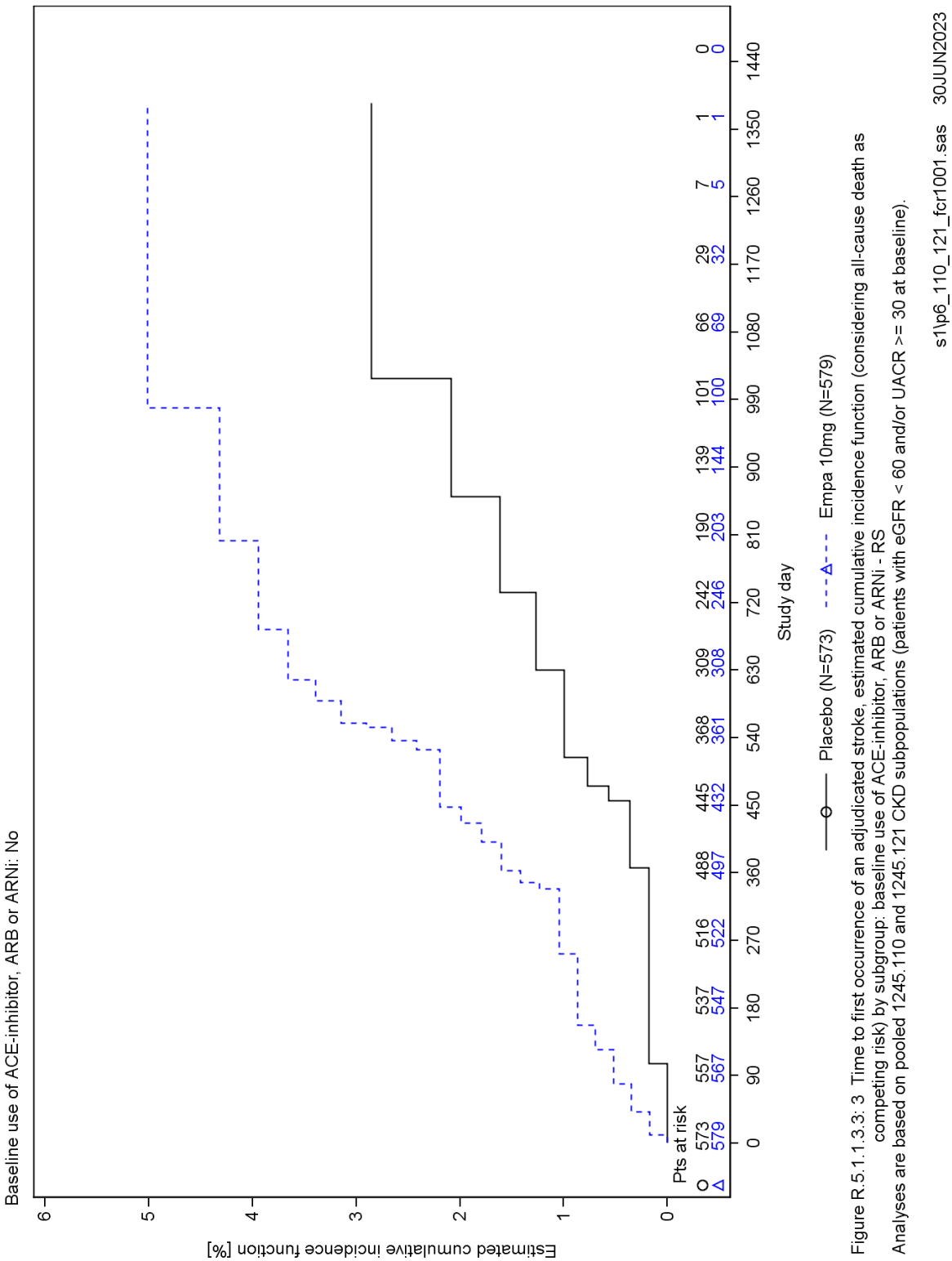


Figure R.5.1.1.3.3: 3 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline use of ACE-inhibitor, ARB or ARNi - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**Figure R.5.1.1.3.3: 3**

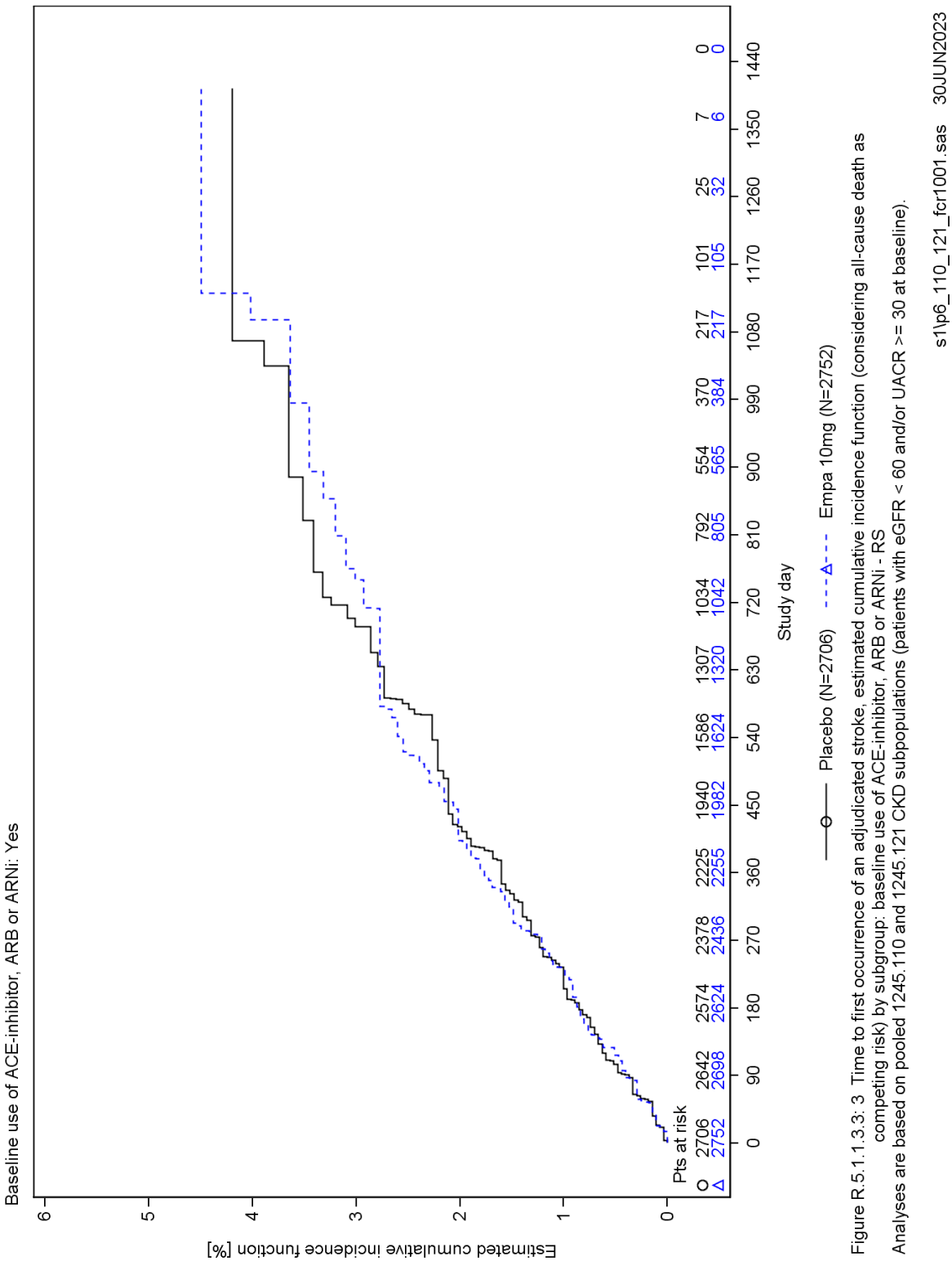


Figure R.5.1.1.3.3: 3 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline use of ACE-inhibitor, ARB or ARNi - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.3: 4**

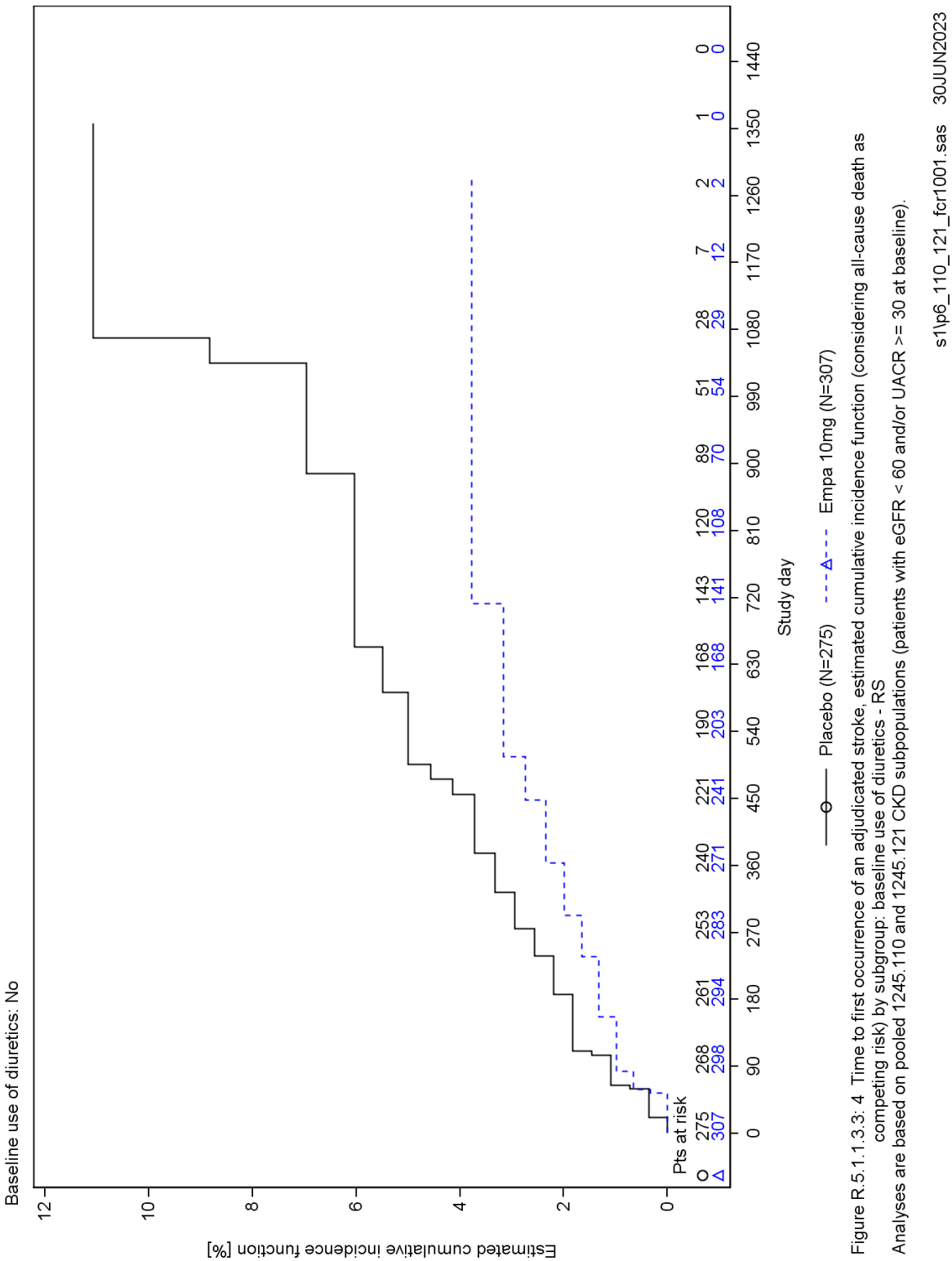


Figure R.5.1.1.3.3: 4 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline use of diuretics - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

s1\p6_110_121_fcr1001.sas 30JUN2023

**Figure R.5.1.1.3.3: 4**

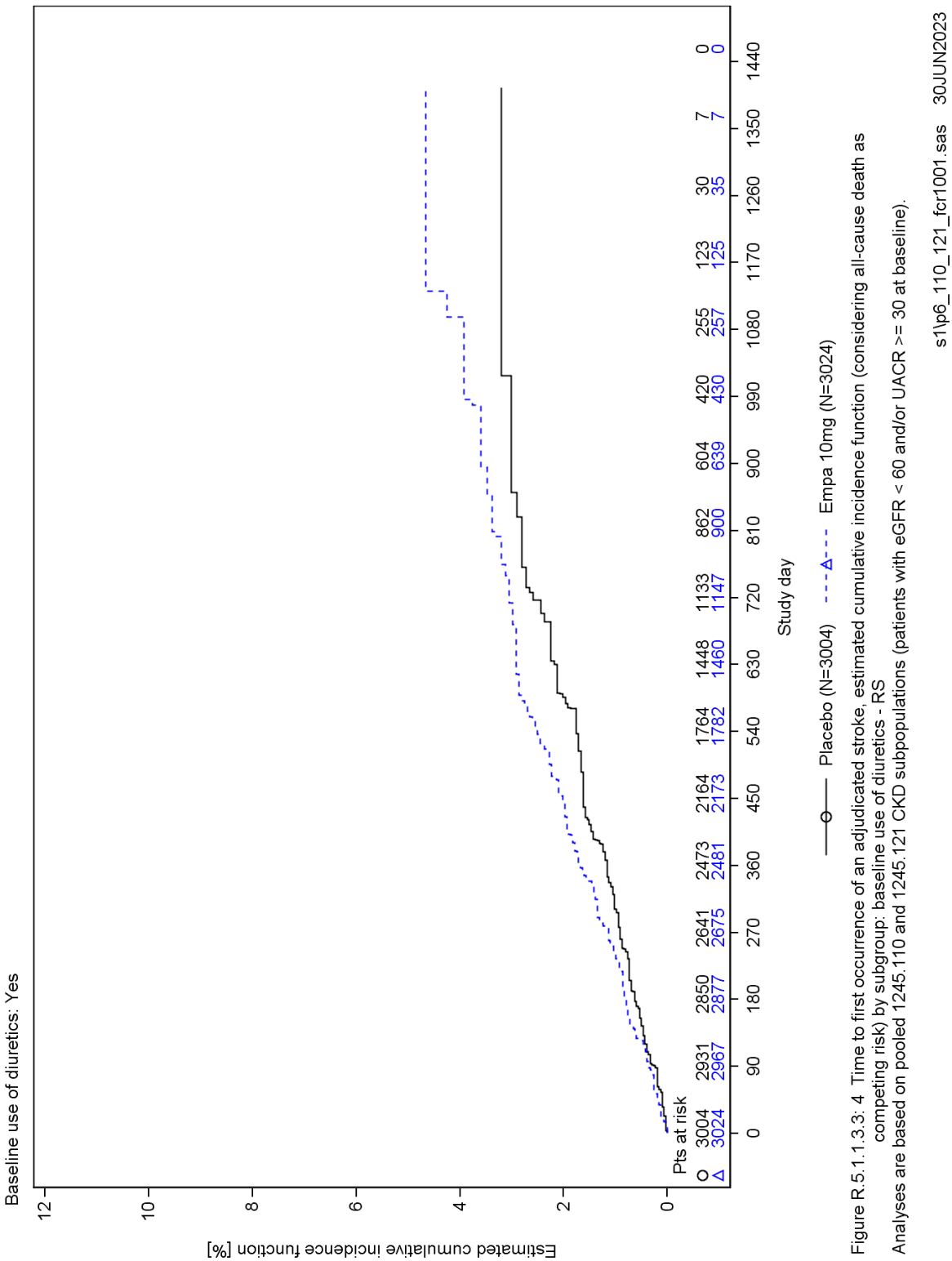


Figure R.5.1.1.3.3: 4 Time to first occurrence of an adjudicated stroke, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline use of diuretics - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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R.5.1.1.3.4 Time to first adjudicated hospitalization for heart failure

**Figure R.5.1.1.3.4: 1**

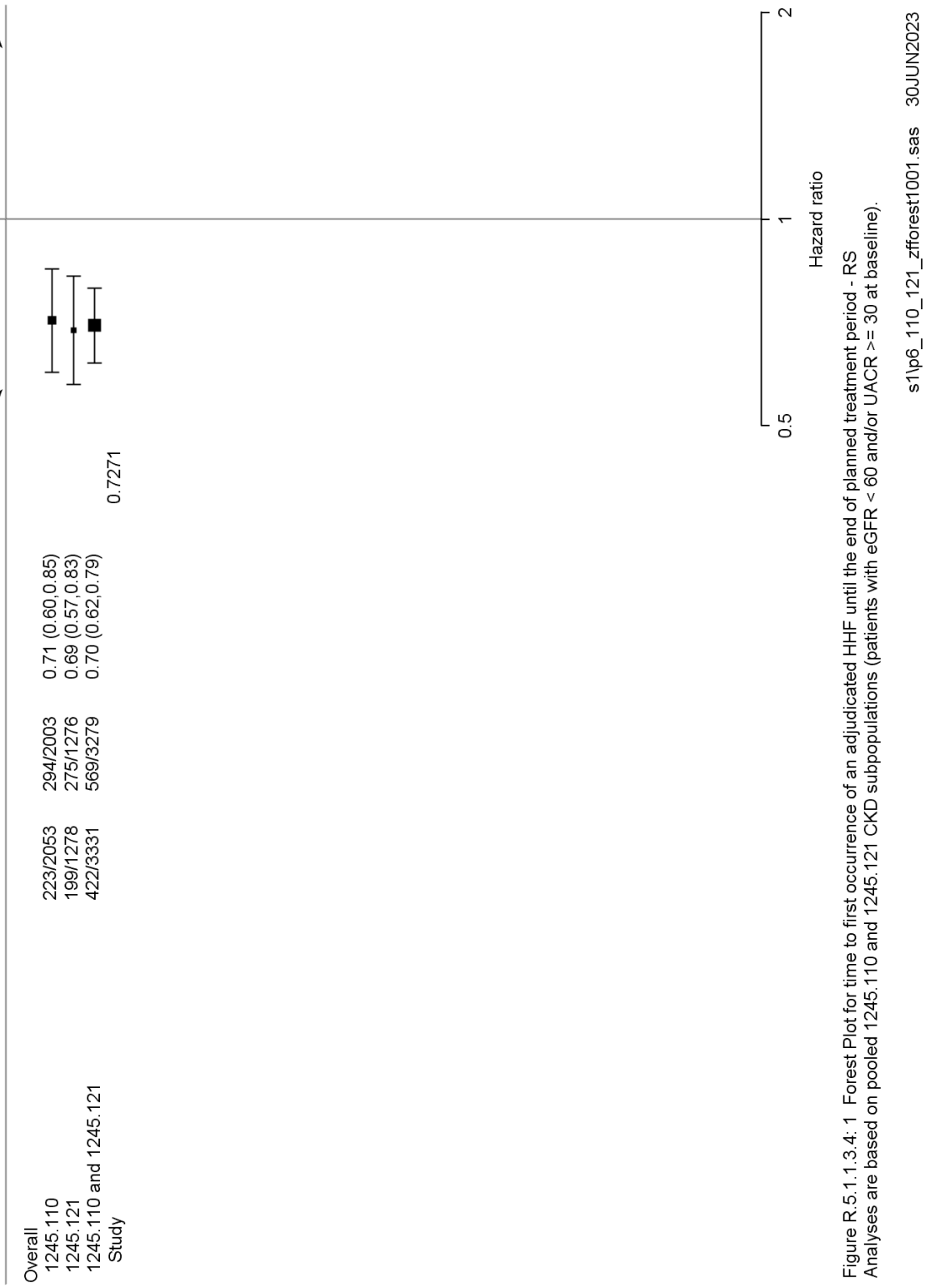


Figure R.5.1.1.3.4: 1 Forest Plot for time to first occurrence of an adjudicated HHF until the end of planned treatment period - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3279 | 569 | 17.4 | 10.76 | 3331 | 422 | 12.7 | 7.54 | 0.70 | (0.62,0.79) | <0.0001 | |
| Study | | | | | | | | | | | | 0.7271 |
| Sex | | | | | | | | | | | | 0.2506 |
| Male | 2024 | 377 | 18.6 | 12.15 | 2069 | 298 | 14.4 | 8.99 | 0.73 | (0.63,0.86) | <0.0001 | |
| Female | 1255 | 192 | 15.3 | 8.79 | 1262 | 124 | 9.8 | 5.43 | 0.63 | (0.50,0.79) | <0.0001 | |
| Age [years] | | | | | | | | | | | | 0.9388 |
| <65 | 767 | 156 | 20.3 | 13.90 | 705 | 107 | 15.2 | 9.94 | 0.71 | (0.55,0.90) | 0.0058 | |
| >=65 | 2512 | 413 | 16.4 | 9.92 | 2626 | 315 | 12.0 | 6.97 | 0.70 | (0.60,0.81) | <0.0001 | |
| Region | | | | | | | | | | | | 0.3033 |
| North America | 434 | 102 | 23.5 | 14.54 | 433 | 82 | 18.9 | 10.89 | 0.75 | (0.56,1.00) | 0.0504 | |
| Latin America | 931 | 134 | 14.4 | 9.56 | 944 | 102 | 10.8 | 7.02 | 0.73 | (0.56,0.94) | 0.0167 | |
| Europe | 1338 | 204 | 15.2 | 9.00 | 1361 | 154 | 11.3 | 6.46 | 0.72 | (0.58,0.89) | 0.0022 | |
| Asia | 405 | 102 | 25.2 | 16.13 | 413 | 59 | 14.3 | 8.29 | 0.51 | (0.37,0.71) | <0.0001 | |
| Other | 171 | 27 | 15.8 | 9.47 | 180 | 25 | 13.9 | 8.44 | 0.92 | (0.53,1.58) | 0.7565 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.5691 |
| Diabetic | 1742 | 353 | 20.3 | 12.87 | 1780 | 255 | 14.3 | 8.72 | 0.68 | (0.58,0.80) | <0.0001 | |
| Non-Diabetic | 1537 | 216 | 14.1 | 8.49 | 1551 | 167 | 10.8 | 6.25 | 0.73 | (0.60,0.90) | 0.0025 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2296 |
| <30 | 1977 | 347 | 17.6 | 11.32 | 1930 | 229 | 11.9 | 7.25 | 0.65 | (0.55,0.77) | <0.0001 | |
| >=30 | 1302 | 222 | 17.1 | 9.99 | 1401 | 193 | 13.8 | 7.92 | 0.76 | (0.63,0.92) | 0.0057 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.7185 |
| <130 | 1686 | 333 | 19.8 | 13.34 | 1687 | 244 | 14.5 | 9.17 | 0.68 | (0.58,0.81) | <0.0001 | |
| >=130 | 1593 | 236 | 14.8 | 8.45 | 1644 | 178 | 10.8 | 6.06 | 0.72 | (0.59,0.87) | 0.0008 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4641 |
| <75 | 1656 | 301 | 18.2 | 11.53 | 1613 | 228 | 14.1 | 8.63 | 0.75 | (0.63,0.90) | 0.0013 | |
| 75 to <85 | 1006 | 173 | 17.2 | 10.37 | 1085 | 127 | 11.7 | 6.88 | 0.64 | (0.51,0.81) | 0.0001 | |
| >=85 | 617 | 95 | 15.4 | 9.42 | 633 | 67 | 10.6 | 6.04 | 0.65 | (0.47,0.88) | 0.0060 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.3.4: 1 Cox Regression for time to first occurrence of an adjudicated HHF until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4014 |
| <30 | 251 | 67 | 26.7 | 19.44 | 263 | 64 | 24.3 | 16.08 | 0.75 | (0.53,1.06) | 0.1010 | |
| 30 to <45 | 899 | 167 | 18.6 | 11.53 | 909 | 132 | 14.5 | 8.74 | 0.77 | (0.61,0.97) | 0.0251 | |
| >=45 | 2128 | 335 | 15.7 | 9.59 | 2159 | 226 | 10.5 | 6.13 | 0.64 | (0.54,0.76) | <0.0001 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8983 |
| Normal (<30) | 1218 | 151 | 12.4 | 7.35 | 1243 | 112 | 9.0 | 5.10 | 0.70 | (0.55,0.90) | 0.0046 | |
| Microalbuminuria (30 to <=300) | 1549 | 282 | 18.2 | 11.44 | 1547 | 209 | 13.5 | 8.14 | 0.72 | (0.60,0.86) | 0.0003 | |
| Macroalbuminuria (>300) | 500 | 132 | 26.4 | 17.52 | 525 | 101 | 19.2 | 12.52 | 0.67 | (0.51,0.86) | 0.0022 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3014 |
| Low, moderate or high | 2432 | 362 | 14.9 | 9.04 | 2496 | 258 | 10.3 | 6.01 | 0.67 | (0.57,0.79) | <0.0001 | |
| Very high | 836 | 203 | 24.3 | 15.98 | 820 | 164 | 20.0 | 12.79 | 0.77 | (0.63,0.95) | 0.0135 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.3186 |
| No | 573 | 113 | 19.7 | 11.87 | 579 | 95 | 16.4 | 9.51 | 0.79 | (0.60,1.04) | 0.0921 | |
| Yes | 2706 | 456 | 16.9 | 10.52 | 2752 | 327 | 11.9 | 7.11 | 0.68 | (0.59,0.78) | <0.0001 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4583 |
| No | 344 | 55 | 16.0 | 9.20 | 349 | 44 | 12.6 | 7.34 | 0.81 | (0.54,1.20) | 0.2871 | |
| Yes | 2935 | 514 | 17.5 | 10.96 | 2982 | 378 | 12.7 | 7.56 | 0.69 | (0.60,0.79) | <0.0001 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.3110 |
| No | 275 | 20 | 7.3 | 3.77 | 307 | 10 | 3.3 | 1.73 | 0.47 | (0.22,1.01) | 0.0542 | |
| Yes | 3004 | 549 | 18.3 | 11.54 | 3024 | 412 | 13.6 | 8.21 | 0.71 | (0.62,0.80) | <0.0001 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.4: 2**

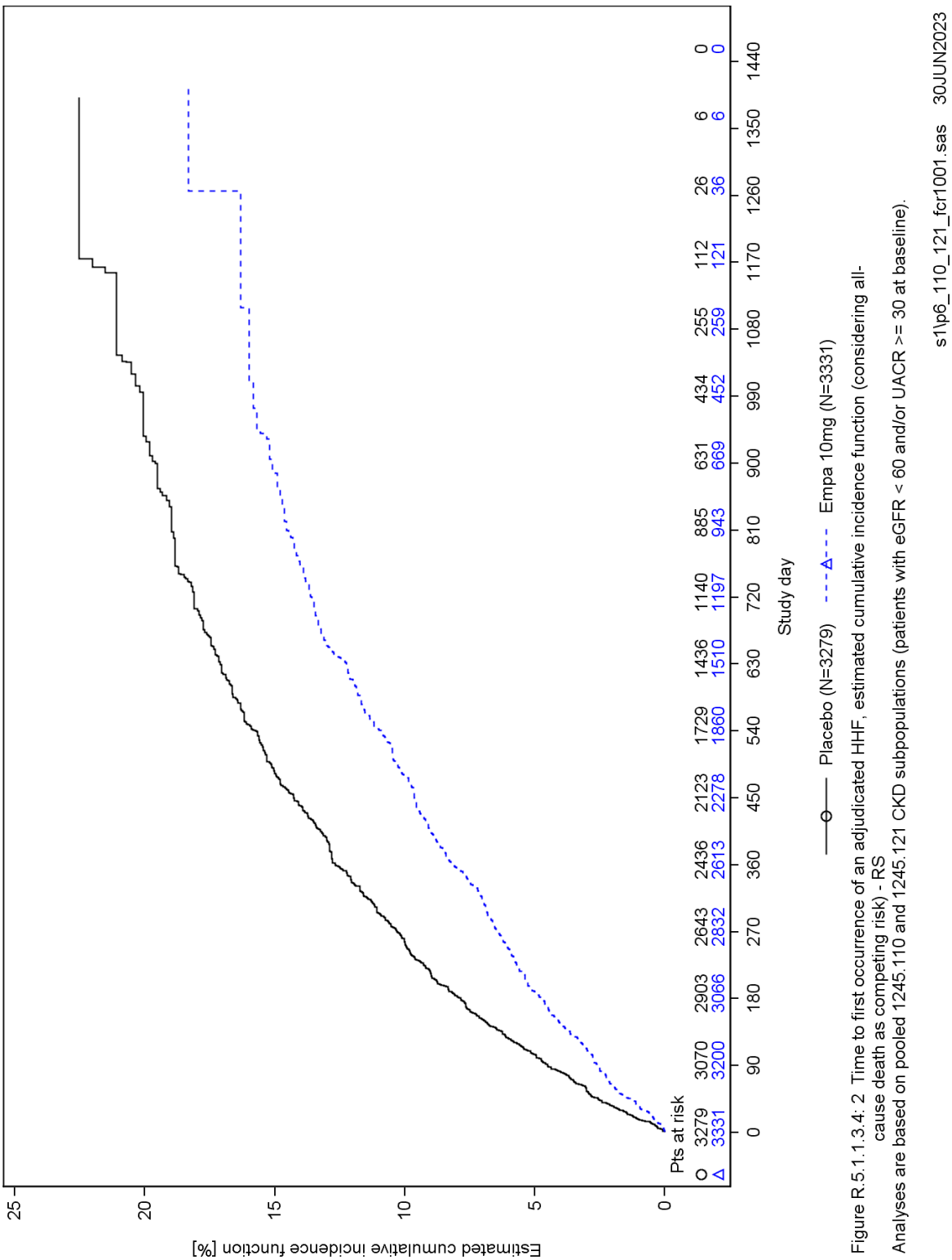


Figure R.5.1.1.3.4: 2 Time to first occurrence of an adjudicated HHF, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

R.5.1.1.3.5 Time to occurrence of adjudicated hospitalization for heart failure (first and recurrent)

**Figure R.5.1.1.3.5: 1**

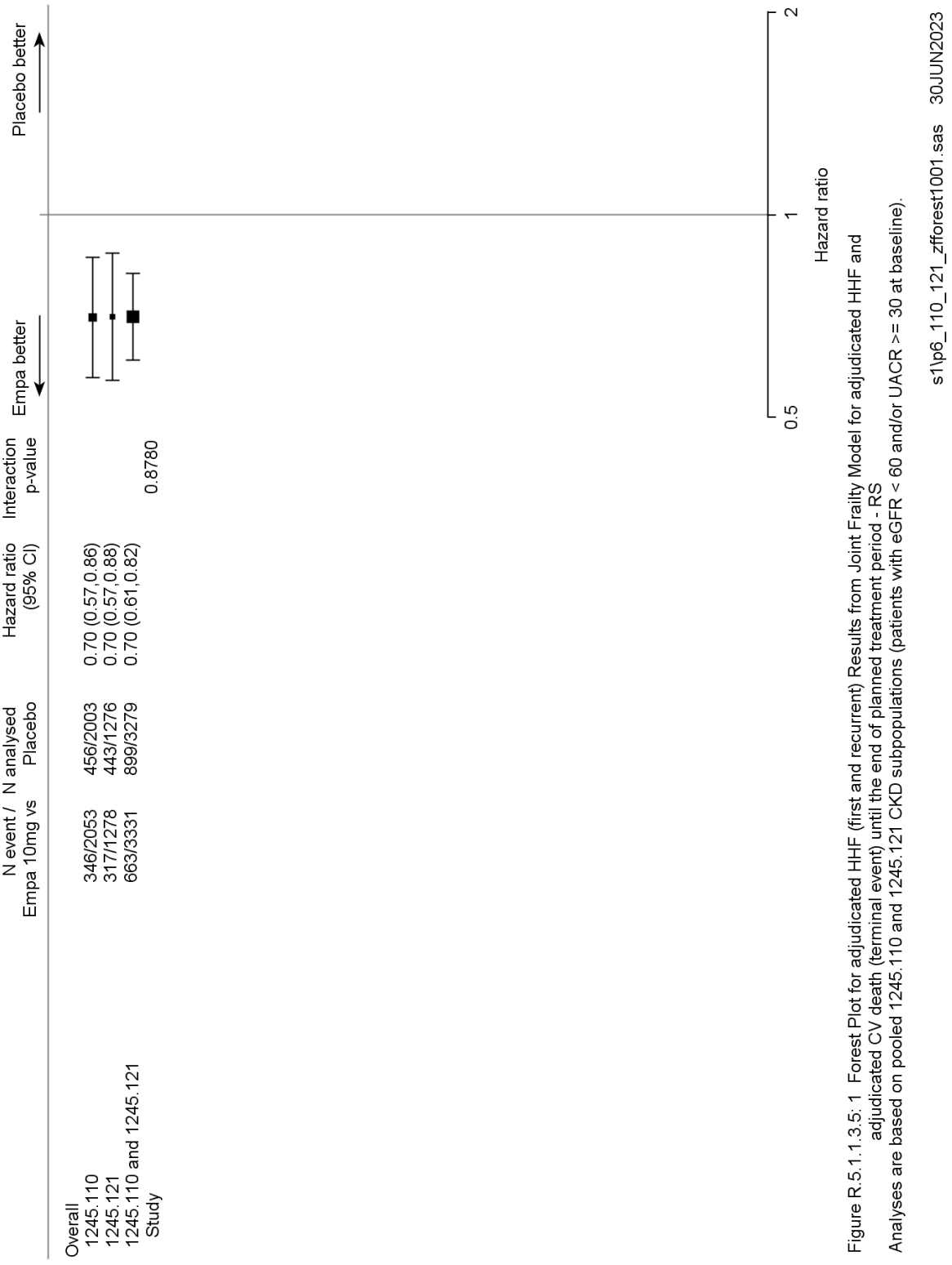


Figure R.5.1.1.3.5: 1 Forest Plot for adjudicated HHF (first and recurrent) Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) until the end of planned treatment period - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | p-value |
| Overall | 3279 | 569 | 17.4 | 899 | 15.39 | 3331 | 422 | 12.7 | 663 | 11.14 | 0.70 | (0.61,0.82) | <0.0001 | |
| Study | | | | | | | | | | | | | | 0.8780 |
| Sex | | | | | | | | | | | | | | 0.2249 |
| Male | 2024 | 377 | 18.6 | 610 | 17.59 | 2069 | 298 | 14.4 | 477 | 13.40 | 0.75 | (0.63,0.91) | 0.0026 | |
| Female | 1255 | 192 | 15.3 | 289 | 12.19 | 1262 | 124 | 9.8 | 186 | 7.78 | 0.62 | (0.48,0.80) | 0.0003 | |
| Age [years] | | | | | | | | | | | | | | 0.2519 |
| <65 | 767 | 156 | 20.3 | 249 | 19.62 | 705 | 107 | 15.2 | 169 | 14.44 | 0.82 | (0.61,1.12) | 0.2117 | |
| >=65 | 2512 | 413 | 16.4 | 650 | 14.22 | 2626 | 315 | 12.0 | 494 | 10.33 | 0.67 | (0.57,0.80) | <0.0001 | |
| Region | | | | | | | | | | | | | | 0.0230 |
| North America | 434 | 102 | 23.5 | 155 | 19.08 | 433 | 82 | 18.9 | 160 | 19.28 | 1.01 | (0.70,1.46) | 0.9462 | |
| Latin America | 931 | 134 | 14.4 | 187 | 12.36 | 944 | 102 | 10.8 | 145 | 9.55 | 0.78 | (0.58,1.04) | 0.0936 | |
| Europe | 1338 | 204 | 15.2 | 305 | 12.34 | 1361 | 154 | 11.3 | 217 | 8.61 | 0.65 | (0.51,0.83) | 0.0005 | |
| Asia | 405 | 102 | 25.2 | 210 | 28.62 | 413 | 59 | 14.3 | 100 | 13.06 | 0.44 | (0.30,0.65) | <0.0001 | |
| Other | 171 | 27 | 15.8 | 42 | 13.58 | 180 | 25 | 13.9 | 41 | 12.93 | 0.98 | (0.52,1.85) | 0.9534 | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9471 |
| Diabetic | 1742 | 353 | 20.3 | 568 | 18.32 | 1780 | 255 | 14.3 | 412 | 13.07 | 0.71 | (0.58,0.86) | 0.0005 | |
| Non-Diabetic | 1537 | 216 | 14.1 | 331 | 12.08 | 1551 | 167 | 10.8 | 251 | 8.97 | 0.71 | (0.57,0.90) | 0.0036 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1373 |
| <30 | 1977 | 347 | 17.6 | 557 | 16.48 | 1930 | 229 | 11.9 | 363 | 10.87 | 0.64 | (0.53,0.78) | <0.0001 | |
| >=30 | 1302 | 222 | 17.1 | 342 | 13.91 | 1401 | 193 | 13.8 | 300 | 11.49 | 0.80 | (0.64,1.01) | 0.0623 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7462 |
| <130 | 1686 | 333 | 19.8 | 530 | 18.92 | 1687 | 244 | 14.5 | 392 | 13.77 | 0.72 | (0.59,0.88) | 0.0014 | |
| >=130 | 1593 | 236 | 14.8 | 369 | 12.15 | 1644 | 178 | 10.8 | 271 | 8.73 | 0.69 | (0.55,0.86) | 0.0008 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1263 |
| <75 | 1656 | 301 | 18.2 | 477 | 16.52 | 1613 | 228 | 14.1 | 377 | 13.38 | 0.80 | (0.65,0.99) | 0.0376 | |
| 75 to <85 | 1006 | 173 | 17.2 | 272 | 14.80 | 1085 | 127 | 11.7 | 183 | 9.34 | 0.56 | (0.43,0.74) | <0.0001 | |
| >=85 | 617 | 95 | 15.4 | 150 | 13.46 | 633 | 67 | 10.6 | 103 | 8.77 | 0.70 | (0.49,0.99) | 0.0459 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline LVEF, baseline diabetes status, subgroup, region, sex, study, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.3.5: 1 Adjudicated HHF (first and recurrent) - Results from Joint Frailty Model for adjudicated HHF and adjudicated CV death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | Interaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1539 |
| <30 | 251 | 67 | 26.7 | 114 | 28.16 | 263 | 64 | 24.3 | 92 | 20.60 | 0.61 | (0.38,0.98) | 0.0409 | |
| 30 to <45 | 899 | 167 | 18.6 | 243 | 15.08 | 909 | 132 | 14.5 | 214 | 13.17 | 0.89 | (0.67,1.17) | 0.3986 | |
| >=45 | 2128 | 335 | 15.7 | 542 | 14.19 | 2159 | 226 | 10.5 | 357 | 9.20 | 0.65 | (0.54,0.79) | <0.0001 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5315 |
| Normal (<30) | 1218 | 151 | 12.4 | 231 | 10.51 | 1243 | 112 | 9.0 | 169 | 7.42 | 0.69 | (0.53,0.90) | 0.0061 | |
| Microalbuminuria (30 to <=300) | 1549 | 282 | 18.2 | 434 | 15.89 | 1547 | 209 | 13.5 | 347 | 12.63 | 0.77 | (0.62,0.95) | 0.0147 | |
| Macroalbuminuria (>300) | 500 | 132 | 26.4 | 229 | 25.71 | 525 | 101 | 19.2 | 147 | 16.35 | 0.62 | (0.44,0.86) | 0.0050 | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4912 |
| Low, moderate or high | 2432 | 362 | 14.9 | 569 | 13.06 | 2496 | 258 | 10.3 | 404 | 8.96 | 0.70 | (0.58,0.83) | <0.0001 | |
| Very high | 836 | 203 | 24.3 | 325 | 22.16 | 820 | 164 | 20.0 | 259 | 18.27 | 0.78 | (0.60,1.02) | 0.0688 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3146 |
| No | 573 | 113 | 19.7 | 187 | 17.58 | 579 | 95 | 16.4 | 170 | 15.58 | 0.82 | (0.58,1.14) | 0.2390 | |
| Yes | 2706 | 456 | 16.9 | 712 | 14.91 | 2752 | 327 | 11.9 | 493 | 10.14 | 0.68 | (0.57,0.80) | <0.0001 | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8879 |
| No | 344 | 55 | 16.0 | 96 | 14.79 | 349 | 44 | 12.6 | 70 | 11.02 | 0.73 | (0.46,1.15) | 0.1730 | |
| Yes | 2935 | 514 | 17.5 | 803 | 15.47 | 2982 | 378 | 12.7 | 593 | 11.16 | 0.70 | (0.60,0.82) | <0.0001 | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2185 |
| No | 275 | 20 | 7.3 | 30 | 5.46 | 307 | 10 | 3.3 | 14 | 2.38 | 0.45 | (0.21,0.93) | 0.0322 | |
| Yes | 3004 | 549 | 18.3 | 869 | 16.43 | 3024 | 412 | 13.6 | 649 | 12.10 | 0.72 | (0.62,0.84) | <0.0001 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline LVEF, baseline diabetes status, subgroup, region, sex, study, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.5: 2**

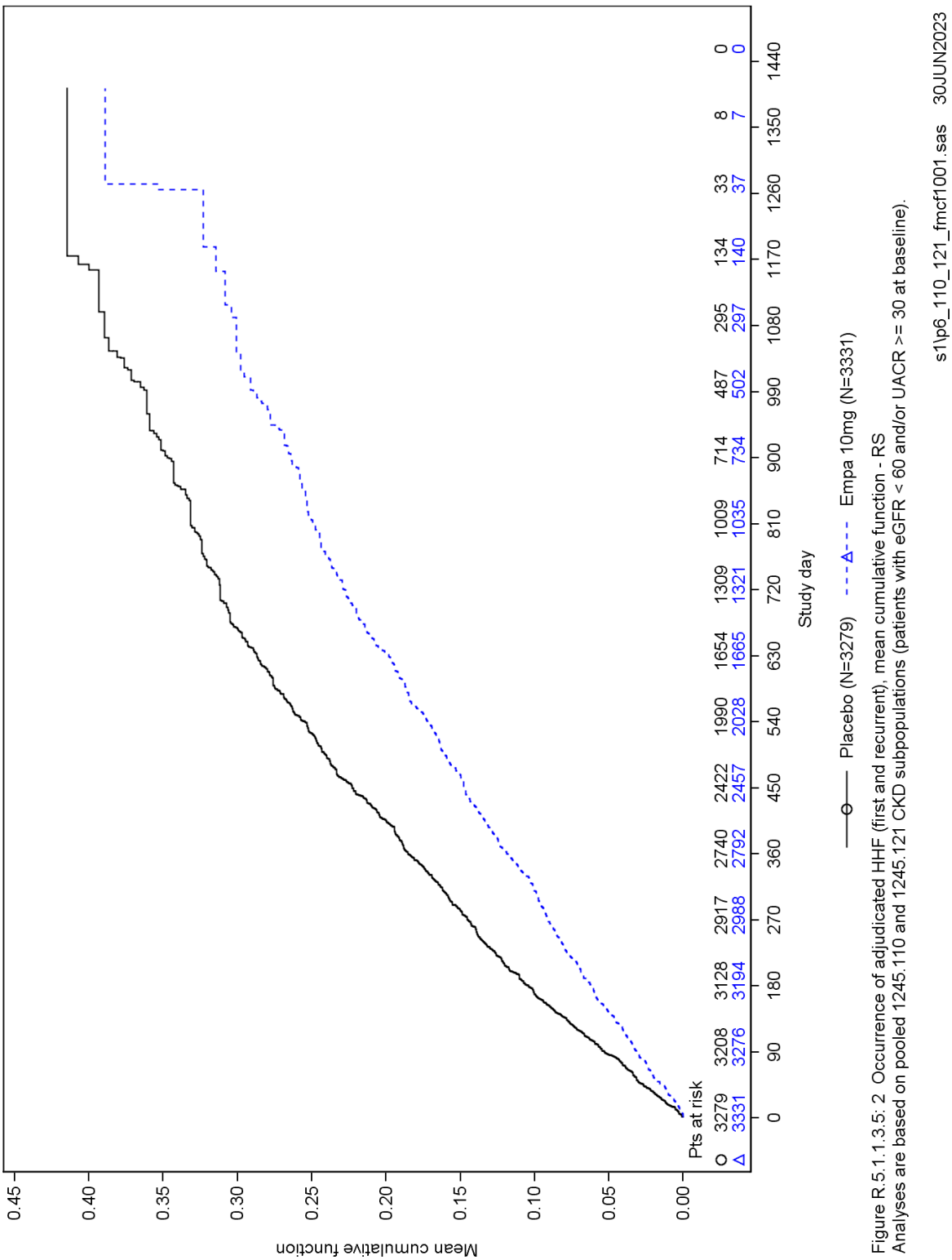


Figure R.5.1.1.3.5: 2 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

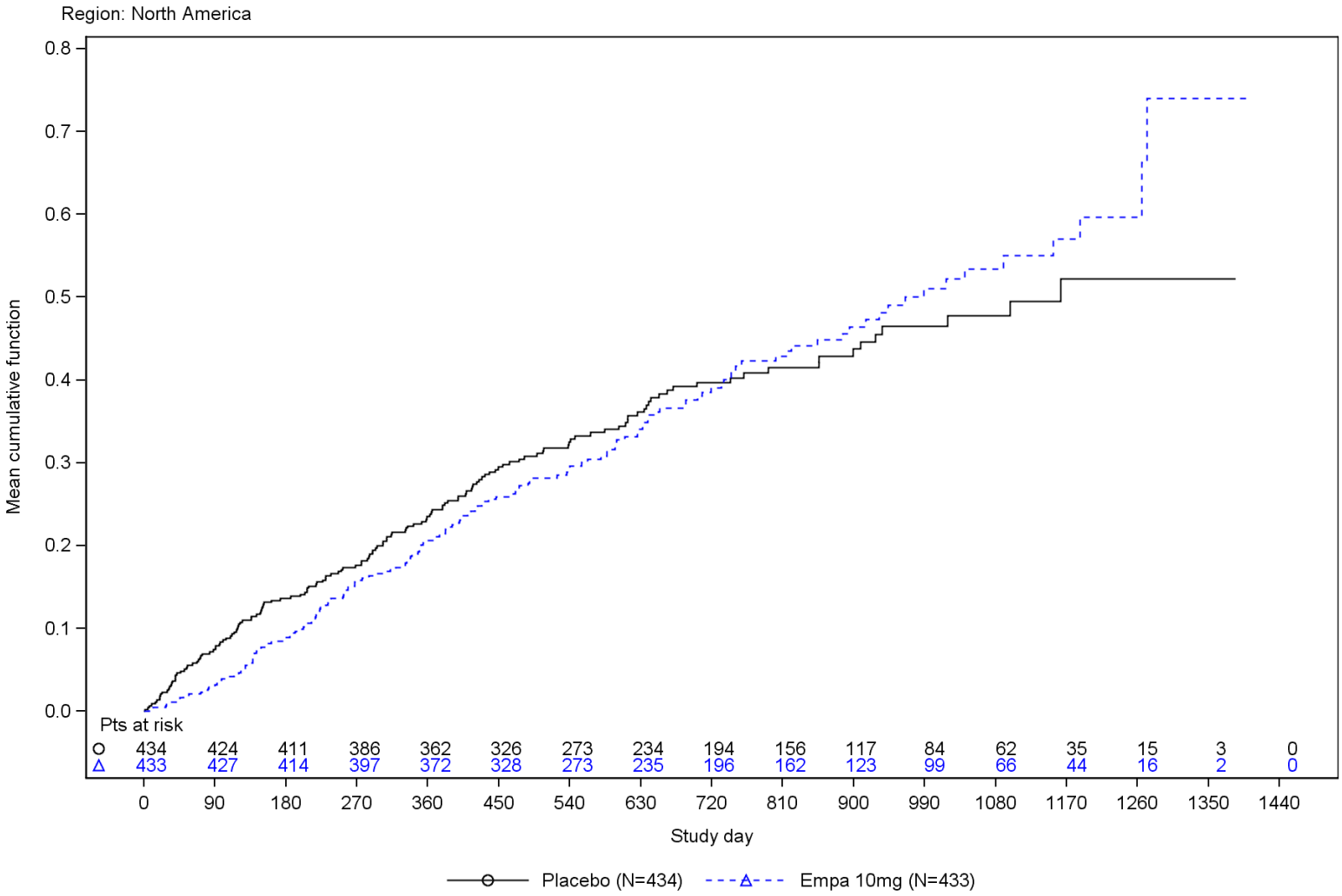


Figure R.5.1.1.3.5: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: region - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**Figure R.5.1.1.3.5: 3**

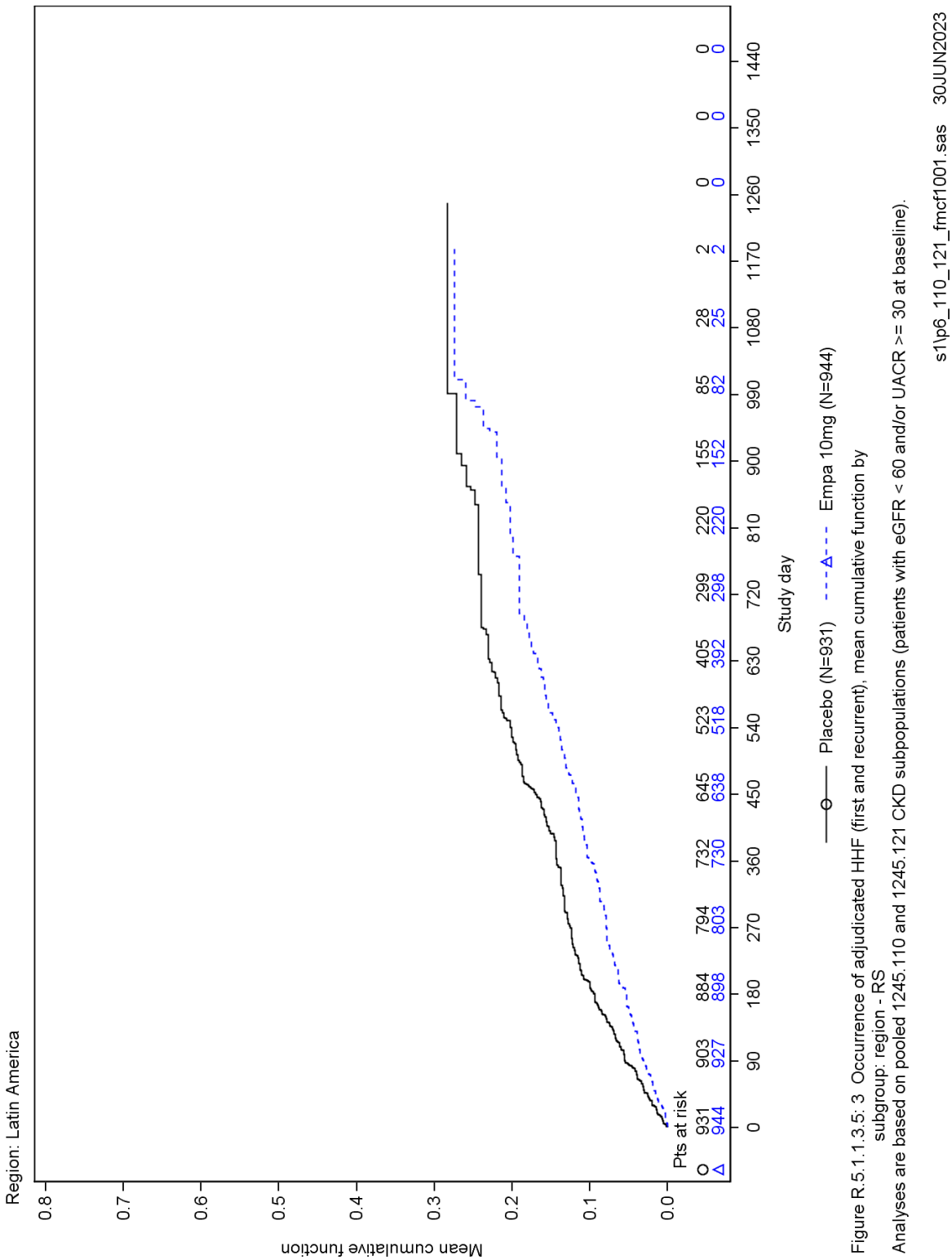


Figure R.5.1.1.3.5: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: region - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.5: 3**

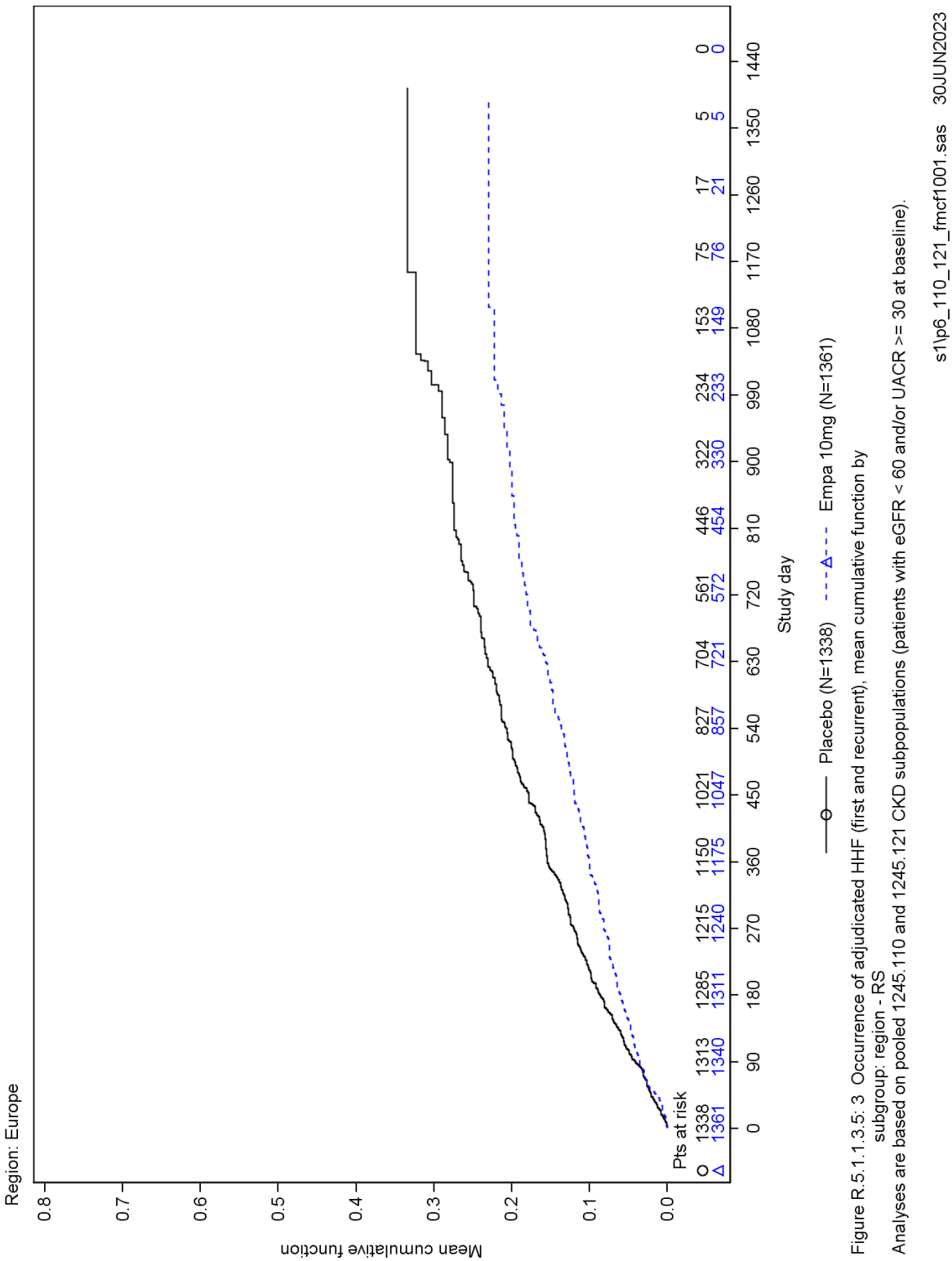


Figure R.5.1.1.3.5: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: region - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.5: 3**

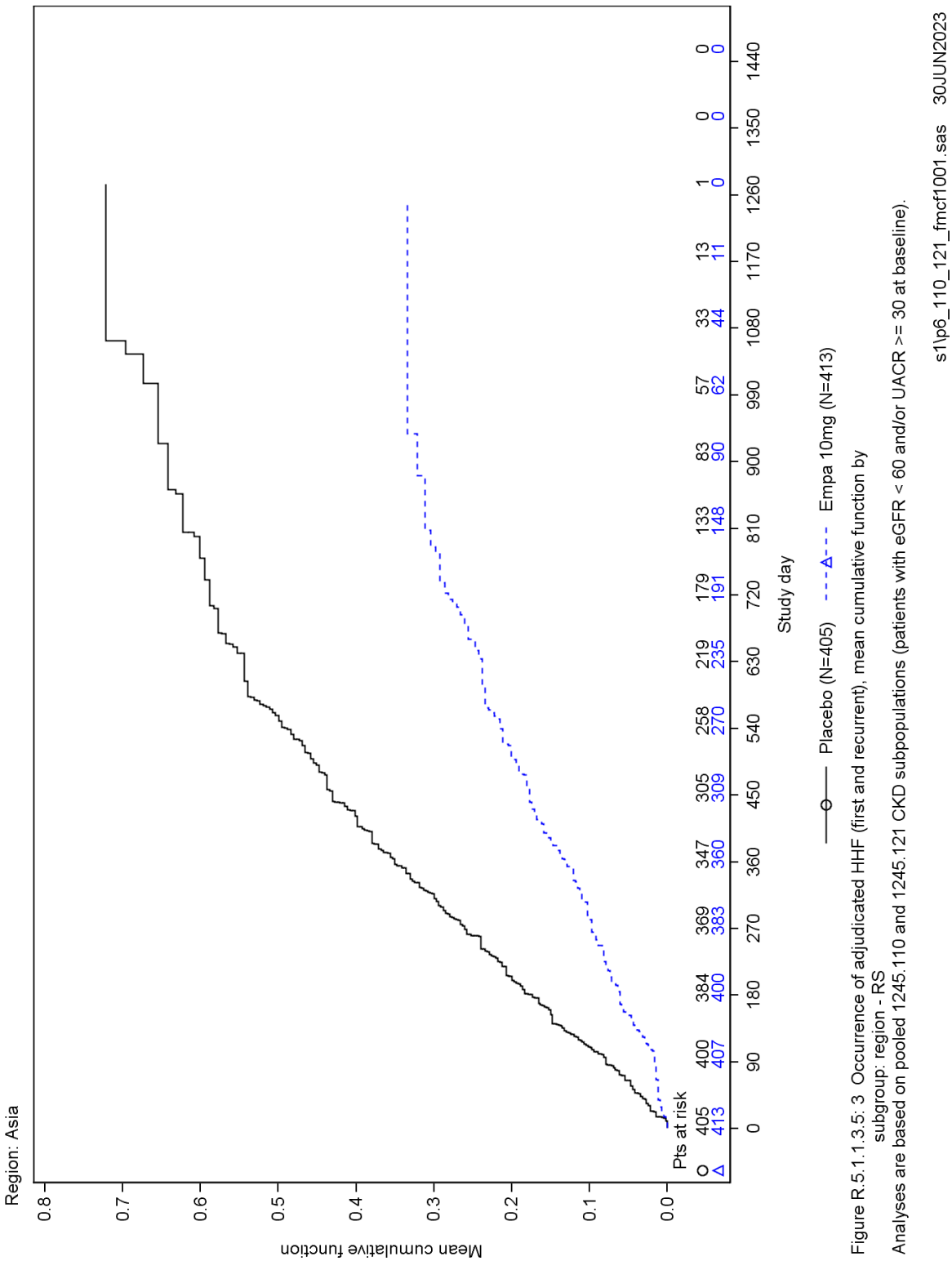


Figure R.5.1.1.3.5: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: region - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.5: 3**

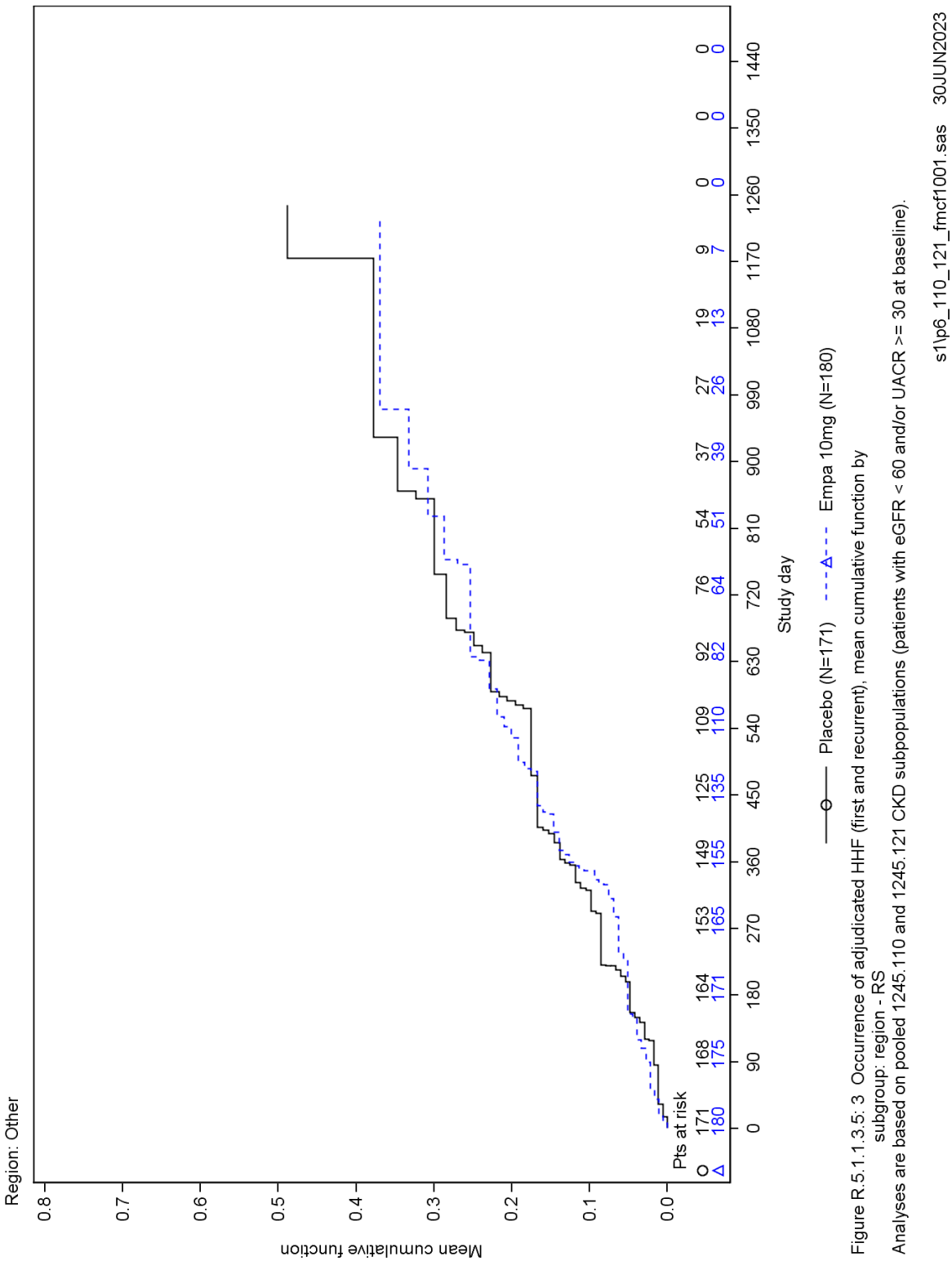


Figure R.5.1.1.3.5: 3 Occurrence of adjudicated HHF (first and recurrent), mean cumulative function by subgroup: region - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**R.5.1.1.3.6**

R.5.1.1.3.6 Time to first occurrence of all-cause hospitalization

**Figure R.5.1.1.3.6: 1**

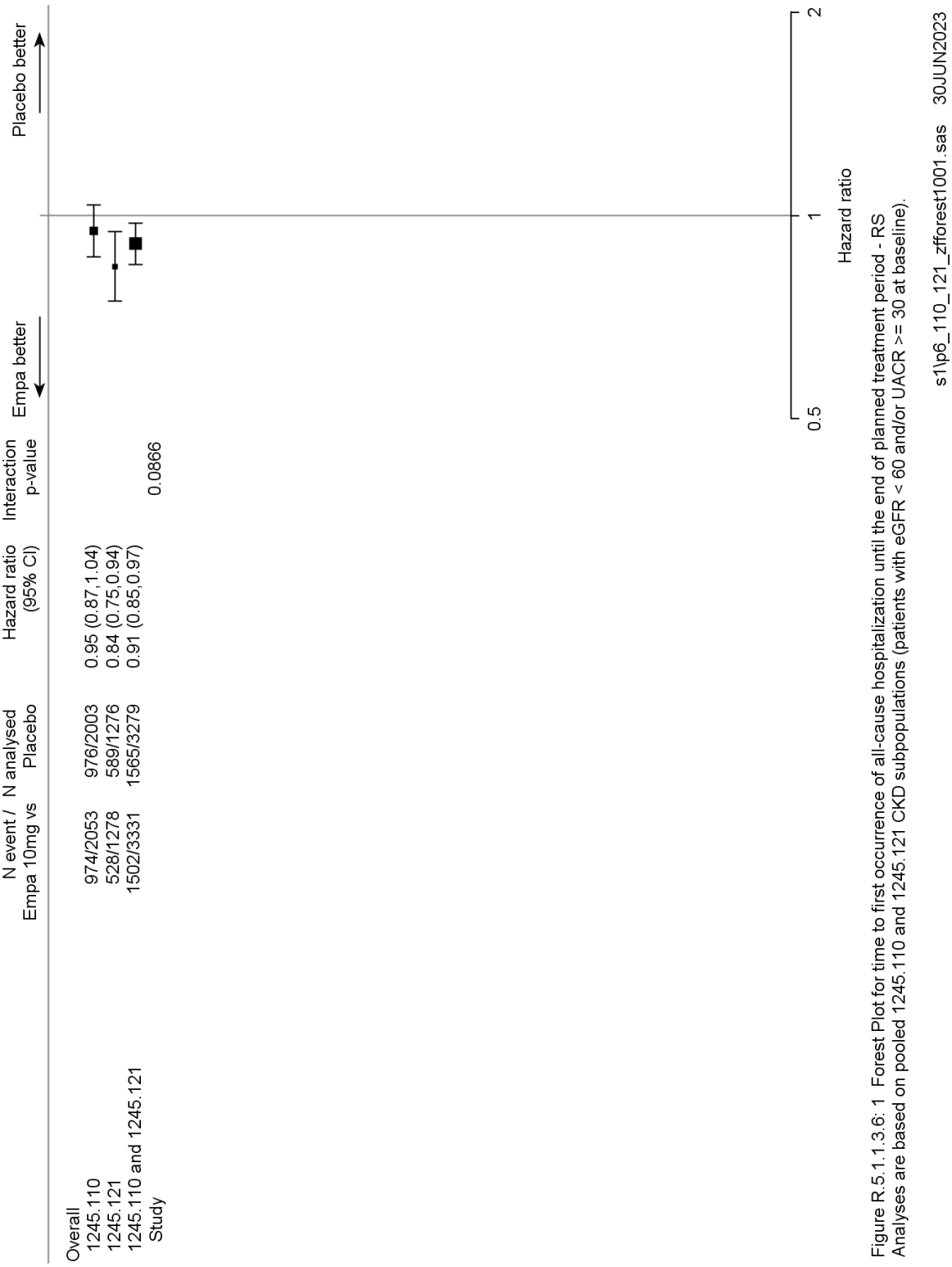


Figure R.5.1.1.3.6: 1 Forest Plot for time to first occurrence of all-cause hospitalization until the end of planned treatment period - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | Empa 10mg | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | Rate^ | N | n | % | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 1565 | 47.7 | 37.72 | 3331 | 1502 | 45.1 | 34.39 | 0.91 | (0.85,0.97) | 0.0070 | |
| Study | | | | | | | | | | | | 0.0866 |
| Sex | | | | | | | | | | | | 0.4225 |
| Male | 2024 | 1009 | 49.9 | 41.83 | 2069 | 966 | 46.7 | 37.40 | 0.89 | (0.81,0.97) | 0.0083 | |
| Female | 1255 | 556 | 44.3 | 32.00 | 1262 | 536 | 42.5 | 30.04 | 0.94 | (0.84,1.06) | 0.3348 | |
| Age [years] | | | | | | | | | | | | 0.8848 |
| <65 | 767 | 337 | 43.9 | 36.36 | 705 | 291 | 41.3 | 33.60 | 0.92 | (0.78,1.07) | 0.2793 | |
| >=65 | 2512 | 1228 | 48.9 | 38.11 | 2626 | 1211 | 46.1 | 34.59 | 0.91 | (0.84,0.98) | 0.0139 | |
| Region | | | | | | | | | | | | 0.0724 |
| North America | 434 | 250 | 57.6 | 49.33 | 433 | 248 | 57.3 | 47.07 | 0.94 | (0.79,1.12) | 0.4852 | |
| Latin America | 931 | 393 | 42.2 | 33.48 | 944 | 360 | 38.1 | 29.31 | 0.87 | (0.75,1.00) | 0.0517 | |
| Europe | 1338 | 619 | 46.3 | 34.91 | 1361 | 631 | 46.4 | 34.80 | 0.99 | (0.89,1.11) | 0.9077 | |
| Asia | 405 | 218 | 53.8 | 45.43 | 413 | 184 | 44.6 | 32.25 | 0.72 | (0.59,0.87) | 0.0009 | |
| Other | 171 | 85 | 49.7 | 39.36 | 180 | 79 | 43.9 | 34.58 | 0.89 | (0.65,1.20) | 0.4400 | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.7124 |
| Diabetic | 1742 | 868 | 49.8 | 40.50 | 1780 | 837 | 47.0 | 36.48 | 0.90 | (0.81,0.99) | 0.0238 | |
| Non-Diabetic | 1537 | 697 | 45.3 | 34.74 | 1551 | 665 | 42.9 | 32.08 | 0.92 | (0.83,1.02) | 0.1271 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0146 |
| <30 | 1977 | 949 | 48.0 | 39.24 | 1930 | 823 | 42.6 | 32.72 | 0.84 | (0.77,0.92) | 0.0003 | |
| >=30 | 1302 | 616 | 47.3 | 35.59 | 1401 | 679 | 48.5 | 36.67 | 1.00 | (0.90,1.12) | 0.9327 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5290 |
| <130 | 1686 | 823 | 48.8 | 41.89 | 1687 | 773 | 45.8 | 37.57 | 0.89 | (0.80,0.98) | 0.0175 | |
| >=130 | 1593 | 742 | 46.6 | 33.97 | 1644 | 729 | 44.3 | 31.57 | 0.93 | (0.84,1.03) | 0.1581 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.1603 |
| <75 | 1656 | 806 | 48.7 | 39.80 | 1613 | 780 | 48.4 | 38.90 | 0.97 | (0.88,1.07) | 0.5352 | |
| 75 to <85 | 1006 | 466 | 46.3 | 35.38 | 1085 | 458 | 42.2 | 31.15 | 0.87 | (0.76,0.99) | 0.0322 | |
| >=85 | 617 | 293 | 47.5 | 36.30 | 633 | 264 | 41.7 | 29.60 | 0.82 | (0.69,0.97) | 0.0178 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.3.6: 1 Cox Regression for time to first occurrence of all-cause hospitalization until the end of planned treatment period overall and by subgroup - RS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Placebo Rate^ | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg Rate^ | Empa 10mg vs Placebo HR* | (95% CI) | p-value | Interaction p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.6632 |
| <30 | 251 | 144 | 57.4 | 54.58 | 263 | 163 | 62.0 | 56.59 | 0.99 | (0.79,1.24) | 0.9179 | |
| 30 to <45 | 899 | 471 | 52.4 | 44.26 | 909 | 435 | 47.9 | 38.16 | 0.88 | (0.77,1.00) | 0.0475 | |
| >=45 | 2128 | 950 | 44.6 | 33.70 | 2159 | 904 | 41.9 | 30.76 | 0.90 | (0.83,0.99) | 0.0316 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.1440 |
| Normal (<30) | 1218 | 527 | 43.3 | 32.59 | 1243 | 535 | 43.0 | 31.49 | 0.97 | (0.86,1.09) | 0.6152 | |
| Microalbuminuria (30 to <=300) | 1549 | 749 | 48.4 | 38.25 | 1547 | 705 | 45.6 | 35.20 | 0.91 | (0.82,1.01) | 0.0846 | |
| Macroalbuminuria (>300) | 500 | 283 | 56.6 | 50.47 | 525 | 259 | 49.3 | 40.22 | 0.79 | (0.67,0.93) | 0.0056 | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.9841 |
| Low, moderate or high | 2432 | 1093 | 44.9 | 34.25 | 2496 | 1058 | 42.4 | 31.24 | 0.91 | (0.84,0.99) | 0.0308 | |
| Very high | 836 | 468 | 56.0 | 49.54 | 820 | 442 | 53.9 | 46.09 | 0.91 | (0.80,1.04) | 0.1679 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6013 |
| No | 573 | 298 | 52.0 | 41.69 | 579 | 297 | 51.3 | 39.16 | 0.94 | (0.80,1.11) | 0.4736 | |
| Yes | 2706 | 1267 | 46.8 | 36.89 | 2752 | 1205 | 43.8 | 33.39 | 0.90 | (0.83,0.97) | 0.0082 | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.8603 |
| No | 344 | 174 | 50.6 | 38.66 | 349 | 160 | 45.8 | 34.49 | 0.89 | (0.72,1.10) | 0.2922 | |
| Yes | 2935 | 1391 | 47.4 | 37.60 | 2982 | 1342 | 45.0 | 34.38 | 0.91 | (0.84,0.98) | 0.0131 | |
| Baseline use of diuretics | | | | | | | | | | | | 0.5095 |
| No | 275 | 122 | 44.4 | 29.84 | 307 | 117 | 38.1 | 25.04 | 0.84 | (0.65,1.08) | 0.1692 | |
| Yes | 3004 | 1443 | 48.0 | 38.58 | 3024 | 1385 | 45.8 | 35.51 | 0.91 | (0.85,0.98) | 0.0180 | |

* Based on a Cox regression model with terms age, baseline eGFR (CKD-EPI), baseline LVEF, study, region, baseline diabetes status, sex, treatment, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n:Number of patients with event, ^Incidence rate, events per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.6: 2**

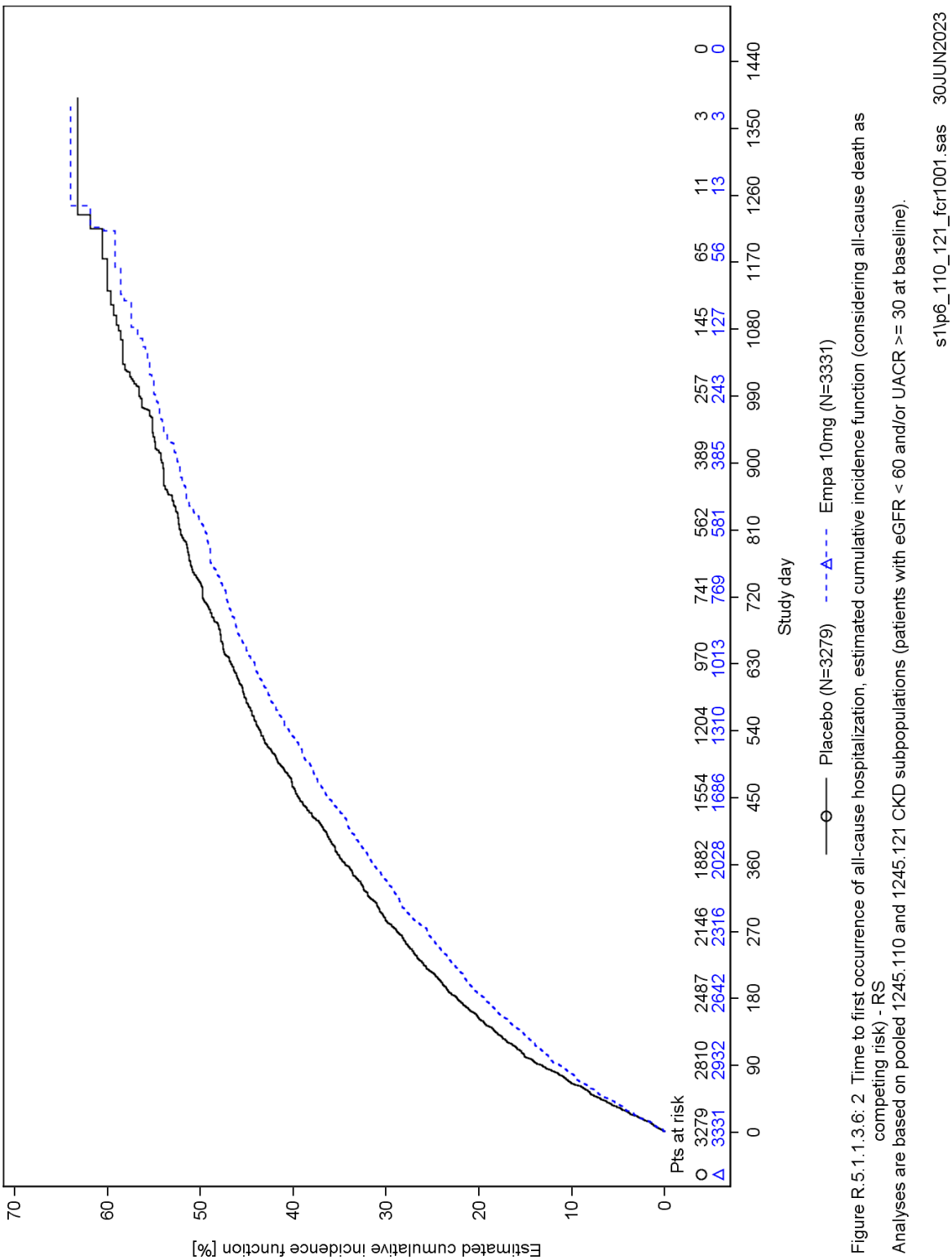


Figure R.5.1.1.3.6: 2 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**Figure R.5.1.1.3.6: 3**

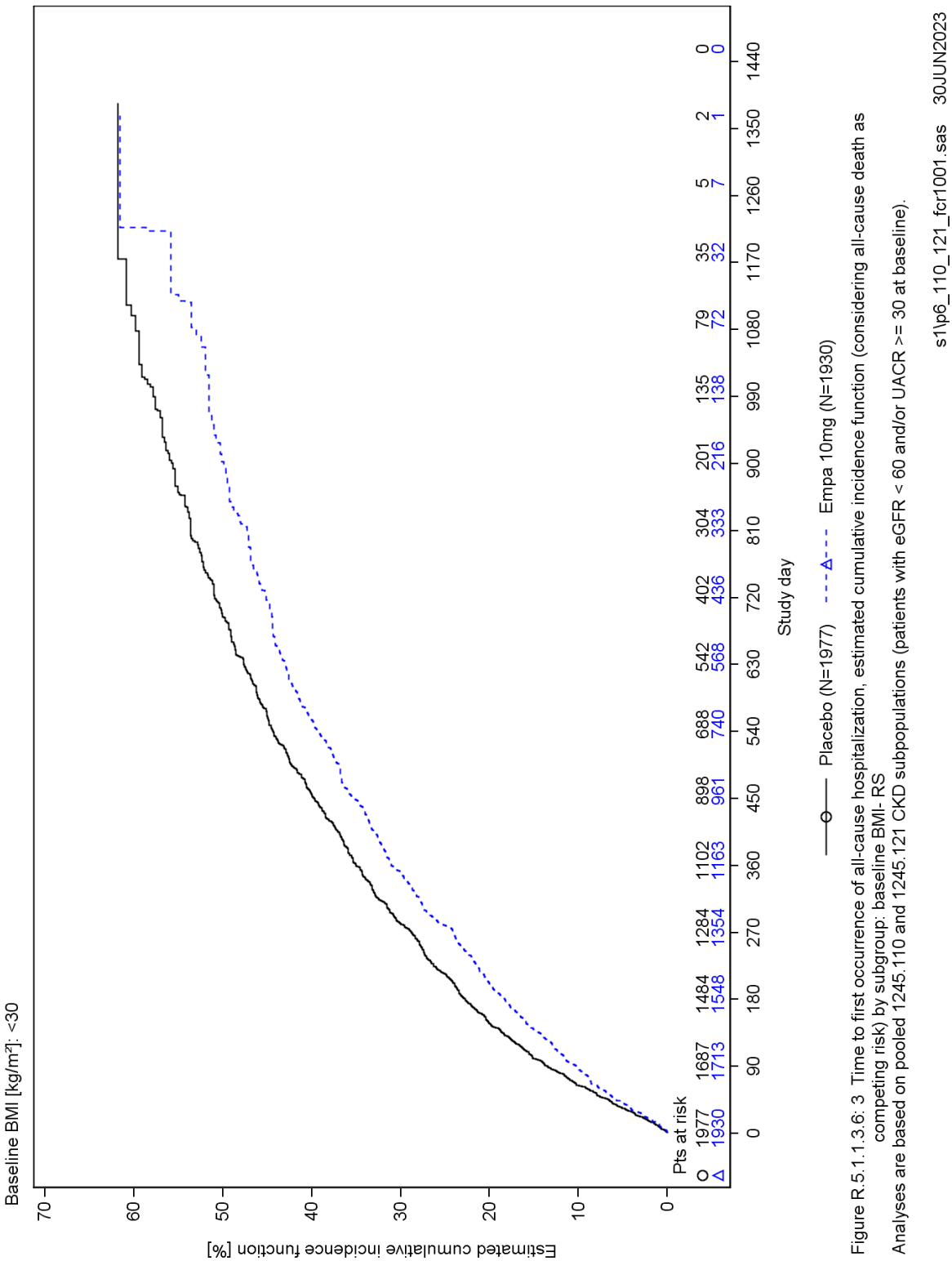


Figure R.5.1.1.3.6: 3 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline BMI- RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**Figure R.5.1.1.3.6: 3**

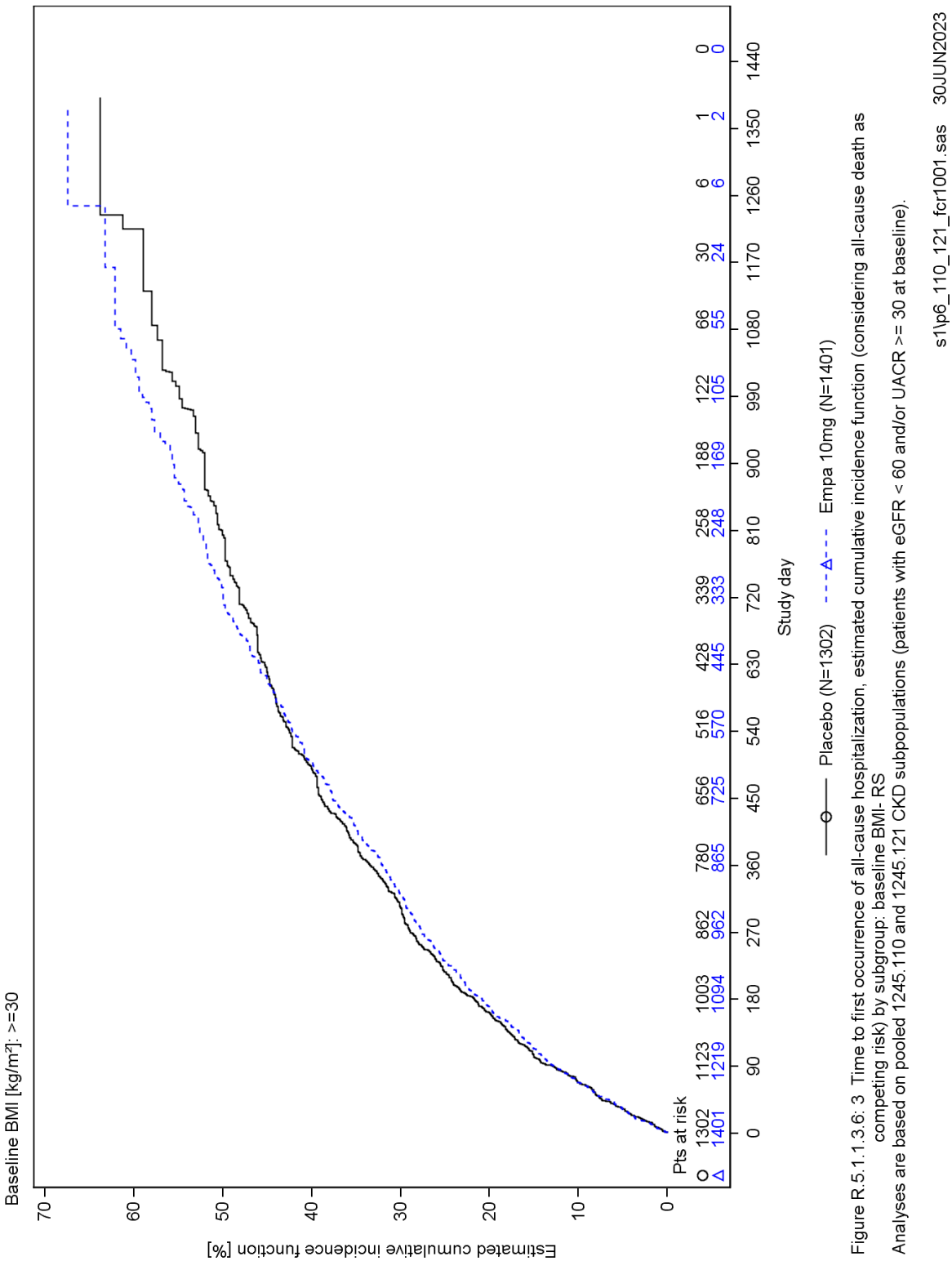


Figure R.5.1.1.3.6: 3 Time to first occurrence of all-cause hospitalization, estimated cumulative incidence function (considering all-cause death as competing risk) by subgroup: baseline BMI- RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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R.5.1.1.3.7 Time to occurrence of all-cause hospitalizations (first and recurrent)

**Figure R.5.1.1.3.7: 1**

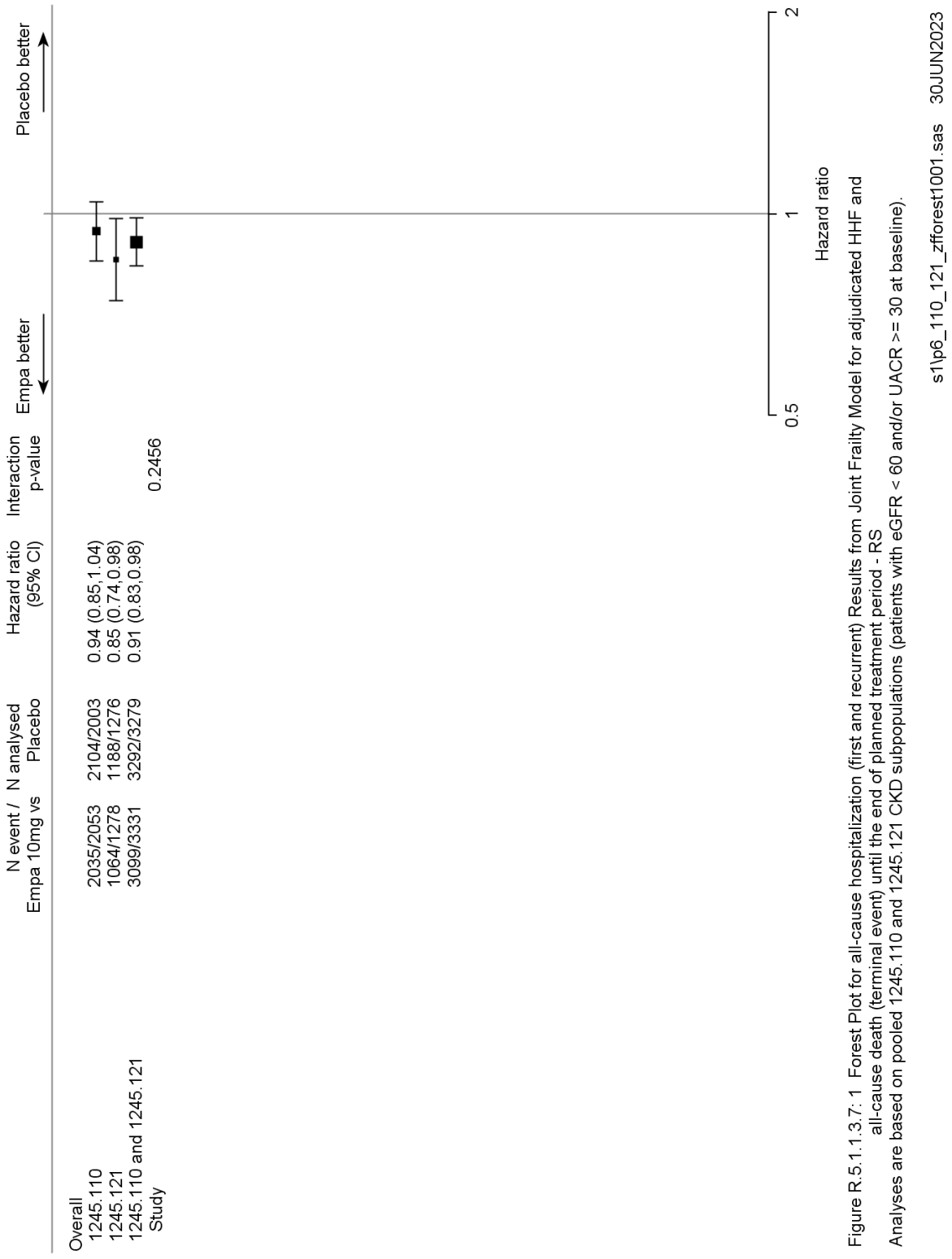


Figure R.5.1.1.3.7: 1 Forest Plot for all-cause hospitalization (first and recurrent) Results from Joint Frailty Model for adjudicated HHF and all-cause death (terminal event) until the end of planned treatment period - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Overall | 3279 | 1565 | 47.7 | 3292 | 56.37 | 3331 | 1502 | 45.1 | 3099 | 52.08 | 0.91 | (0.83,0.98) | 0.0193 | |
| Study | | | | | | | | | | | | | | 0.2456 |
| Sex | | | | | | | | | | | | | | 0.9048 |
| Male | 2024 | 1009 | 49.9 | 2135 | 61.56 | 2069 | 966 | 46.7 | 2034 | 57.15 | 0.91 | (0.82,1.01) | 0.0746 | |
| Female | 1255 | 556 | 44.3 | 1157 | 48.79 | 1262 | 536 | 42.5 | 1065 | 44.52 | 0.90 | (0.79,1.03) | 0.1297 | |
| Age [years] | | | | | | | | | | | | | | 0.5926 |
| <65 | 767 | 337 | 43.9 | 731 | 57.61 | 705 | 291 | 41.3 | 626 | 53.50 | 0.95 | (0.79,1.13) | 0.5403 | |
| >=65 | 2512 | 1228 | 48.9 | 2561 | 56.03 | 2626 | 1211 | 46.1 | 2473 | 51.73 | 0.90 | (0.82,0.98) | 0.0205 | |
| Region | | | | | | | | | | | | | | 0.0338 |
| North America | 434 | 250 | 57.6 | 615 | 75.69 | 433 | 248 | 57.3 | 640 | 77.11 | 1.02 | (0.83,1.27) | 0.8244 | |
| Latin America | 931 | 393 | 42.2 | 668 | 44.14 | 944 | 360 | 38.1 | 580 | 38.20 | 0.86 | (0.72,1.01) | 0.0680 | |
| Europe | 1338 | 619 | 46.3 | 1310 | 53.02 | 1361 | 631 | 46.4 | 1318 | 52.30 | 0.98 | (0.86,1.11) | 0.7457 | |
| Asia | 405 | 218 | 53.8 | 508 | 69.22 | 413 | 184 | 44.6 | 378 | 49.36 | 0.66 | (0.52,0.83) | 0.0004 | |
| Other | 171 | 85 | 49.7 | 191 | 61.75 | 180 | 79 | 43.9 | 183 | 57.71 | 0.93 | (0.66,1.33) | 0.7032 | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9794 |
| Diabetic | 1742 | 868 | 49.8 | 1928 | 62.20 | 1780 | 837 | 47.0 | 1752 | 55.58 | 0.91 | (0.81,1.02) | 0.0912 | |
| Non-Diabetic | 1537 | 697 | 45.3 | 1364 | 49.78 | 1551 | 665 | 42.9 | 1347 | 48.13 | 0.91 | (0.80,1.02) | 0.1153 | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0561 |
| <30 | 1977 | 949 | 48.0 | 1911 | 56.53 | 1930 | 823 | 42.6 | 1672 | 50.05 | 0.85 | (0.76,0.94) | 0.0028 | |
| >=30 | 1302 | 616 | 47.3 | 1381 | 56.16 | 1401 | 679 | 48.5 | 1427 | 54.66 | 1.00 | (0.88,1.13) | 0.9664 | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8489 |
| <130 | 1686 | 823 | 48.8 | 1733 | 61.85 | 1687 | 773 | 45.8 | 1623 | 57.03 | 0.91 | (0.81,1.02) | 0.1229 | |
| >=130 | 1593 | 742 | 46.6 | 1559 | 51.32 | 1644 | 729 | 44.3 | 1476 | 47.54 | 0.90 | (0.80,1.01) | 0.0767 | |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4134 |
| <75 | 1656 | 806 | 48.7 | 1762 | 61.01 | 1613 | 780 | 48.4 | 1664 | 59.04 | 0.96 | (0.85,1.07) | 0.4498 | |
| 75 to <85 | 1006 | 466 | 46.3 | 958 | 52.14 | 1085 | 458 | 42.2 | 911 | 46.52 | 0.87 | (0.75,1.01) | 0.0735 | |
| >=85 | 617 | 293 | 47.5 | 572 | 51.35 | 633 | 264 | 41.7 | 524 | 44.62 | 0.84 | (0.69,1.01) | 0.0670 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline LVEF, baseline diabetes status, subgroup, region, sex, study, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.1.1.3.7: 1 All-cause hospitalizations (first and recurrent) - Results from Joint Frailty Model for all-cause hospitalization and all-cause death (terminal event) until the end of planned treatment period overall and by subgroup - RS

| Subgroup | Placebo | | | | | Empa 10mg | | | | | Empa 10mg vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n¹ | % | n² | Rate^ | N | n¹ | % | n² | Rate^ | HR* | (95% CI) | p-value | Interaction p-value |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4718 |
| <30 | 251 | 144 | 57.4 | 336 | 82.99 | 263 | 163 | 62.0 | 392 | 87.79 | 1.02 | (0.77,1.35) | 0.8978 | |
| 30 to <45 | 899 | 471 | 52.4 | 1019 | 63.22 | 909 | 435 | 47.9 | 944 | 58.11 | 0.95 | (0.81,1.11) | 0.5073 | |
| >=45 | 2128 | 950 | 44.6 | 1937 | 50.70 | 2159 | 904 | 41.9 | 1763 | 45.44 | 0.87 | (0.79,0.97) | 0.0114 | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2624 |
| Normal (<30) | 1218 | 527 | 43.3 | 1080 | 49.13 | 1243 | 535 | 43.0 | 1079 | 47.36 | 0.99 | (0.87,1.14) | 0.9294 | |
| Microalbuminuria (30 to <=300) | 1549 | 749 | 48.4 | 1540 | 56.39 | 1547 | 705 | 45.6 | 1474 | 53.67 | 0.89 | (0.79,1.00) | 0.0519 | |
| Macroalbuminuria (>300) | 500 | 283 | 56.6 | 655 | 73.53 | 525 | 259 | 49.3 | 539 | 59.94 | 0.82 | (0.67,1.01) | 0.0618 | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2474 |
| Low, moderate or high | 2432 | 1093 | 44.9 | 2220 | 50.97 | 2496 | 1058 | 42.4 | 2090 | 46.36 | 0.89 | (0.81,0.98) | 0.0196 | |
| Very high | 836 | 468 | 56.0 | 1061 | 72.35 | 820 | 442 | 53.9 | 1006 | 70.95 | 0.99 | (0.85,1.16) | 0.9326 | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3030 |
| No | 573 | 298 | 52.0 | 658 | 61.86 | 579 | 297 | 51.3 | 683 | 62.58 | 0.99 | (0.82,1.20) | 0.9210 | |
| Yes | 2706 | 1267 | 46.8 | 2634 | 55.15 | 2752 | 1205 | 43.8 | 2416 | 49.72 | 0.89 | (0.81,0.97) | 0.0096 | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.0339 |
| No | 344 | 174 | 50.6 | 420 | 64.72 | 349 | 160 | 45.8 | 306 | 48.17 | 0.70 | (0.54,0.90) | 0.0060 | |
| Yes | 2935 | 1391 | 47.4 | 2872 | 55.33 | 2982 | 1342 | 45.0 | 2793 | 52.54 | 0.94 | (0.86,1.02) | 0.1421 | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2721 |
| No | 275 | 122 | 44.4 | 233 | 42.42 | 307 | 117 | 38.1 | 190 | 32.30 | 0.77 | (0.57,1.04) | 0.0865 | |
| Yes | 3004 | 1443 | 48.0 | 3059 | 57.82 | 3024 | 1385 | 45.8 | 2909 | 54.24 | 0.92 | (0.84,1.00) | 0.0500 | |

* Based on an analysis of recurrent events accounting for terminal events using a joint frailty model with terms for age, baseline eGFR (CKD-EPI), baseline LVEF, baseline diabetes status, subgroup, region, sex, study, treatment and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N:Number of patients analysed, n¹:Number of patients with recurrent event, n²:Number of recurrent events,
^Recurrent event rate, per 100 patient years at risk.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.7: 2**

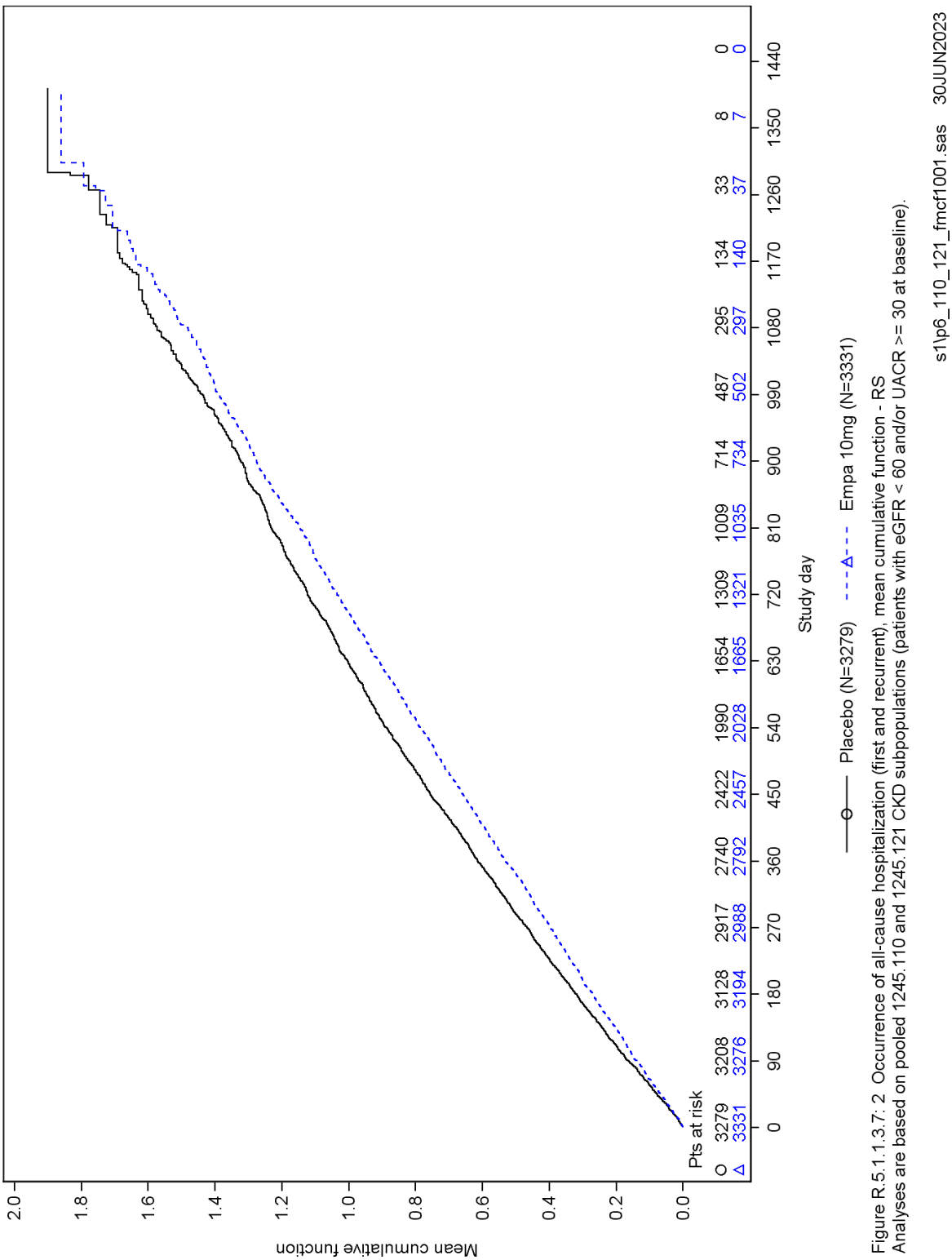


Figure R.5.1.1.3.7: 2 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function - RS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.7: 3**

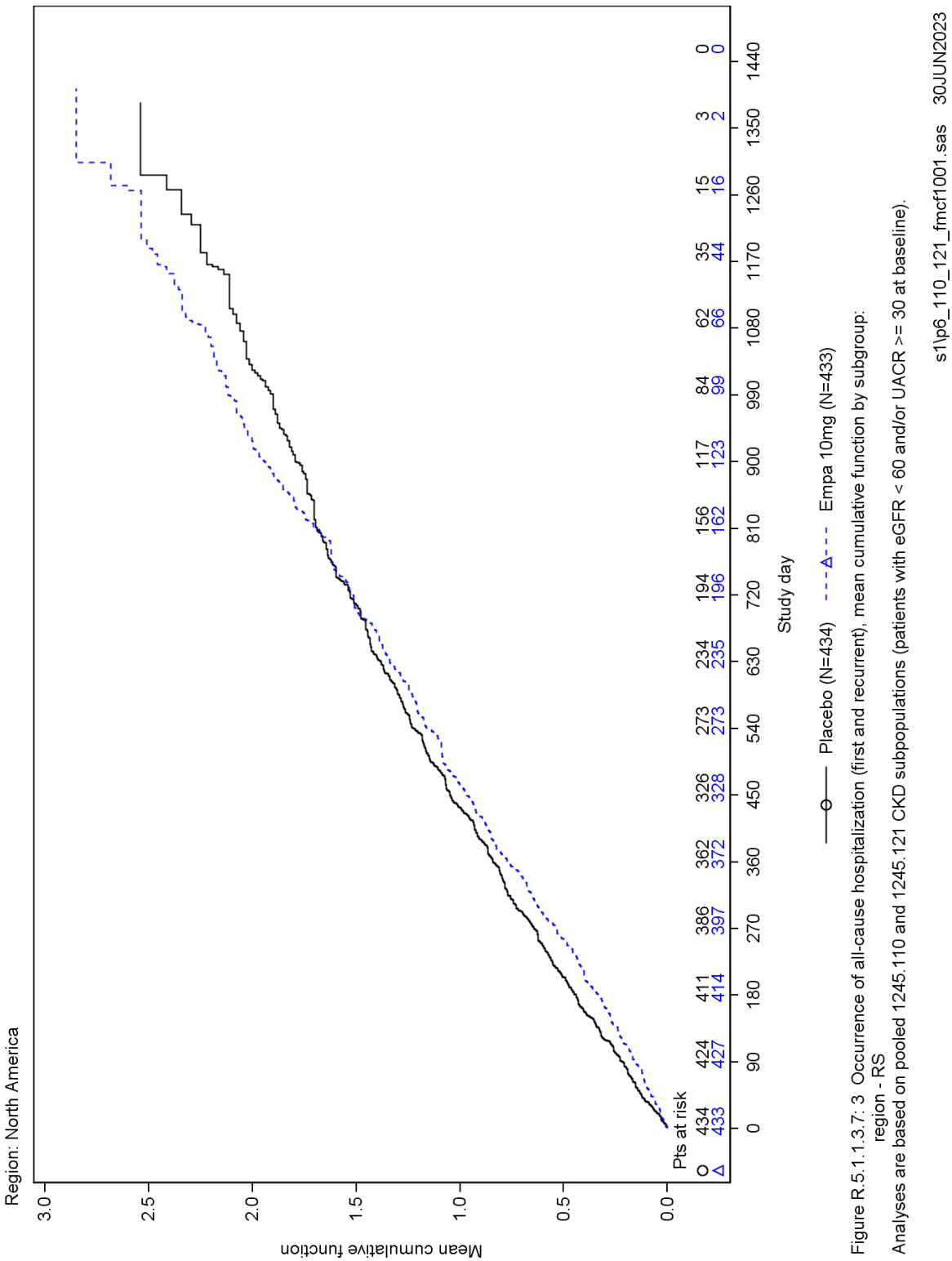


Figure R.5.1.1.3.7: 3 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: region - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**Figure R.5.1.1.3.7: 3**

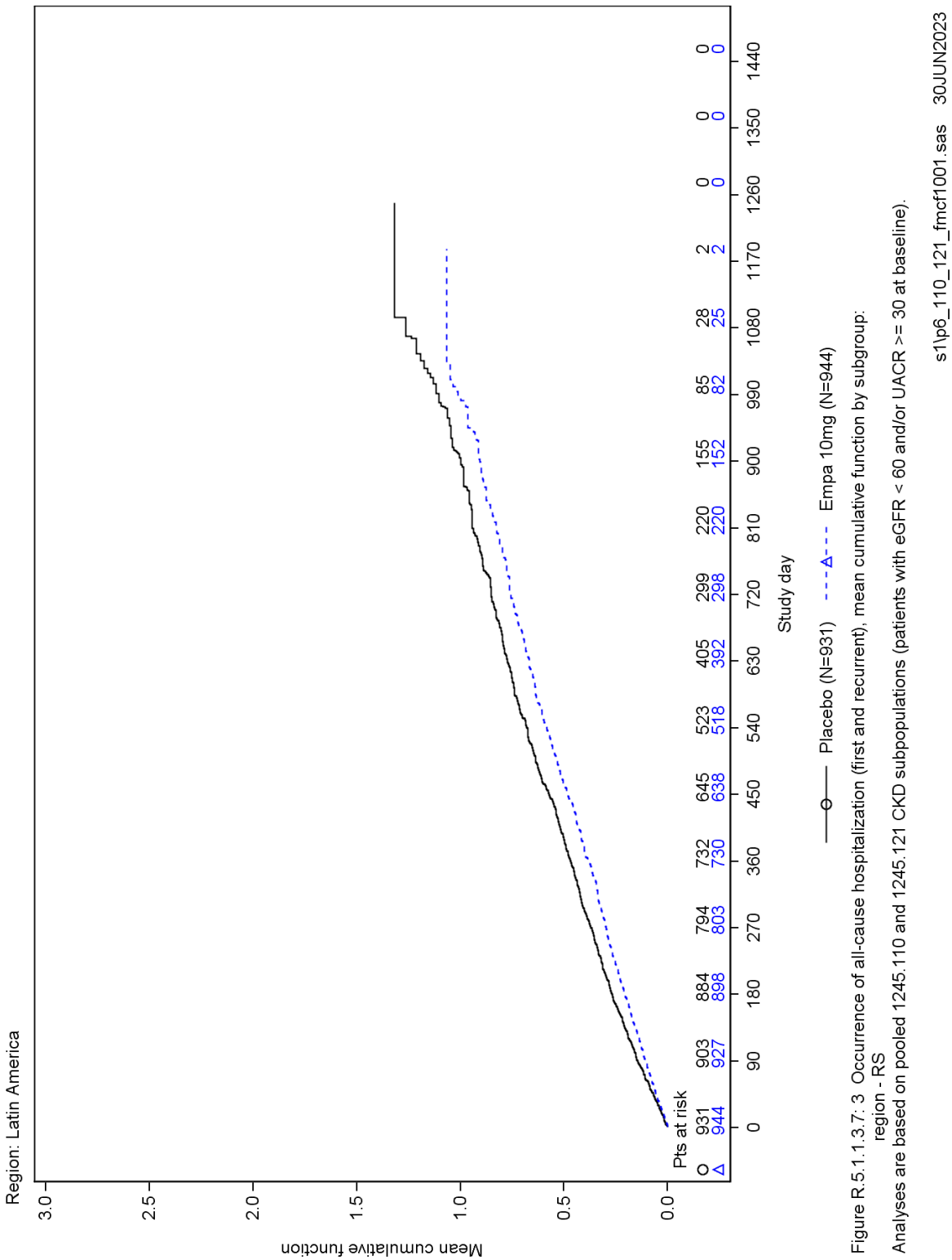


Figure R.5.1.1.3.7: 3 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: region - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

**Figure R.5.1.1.3.7: 3**

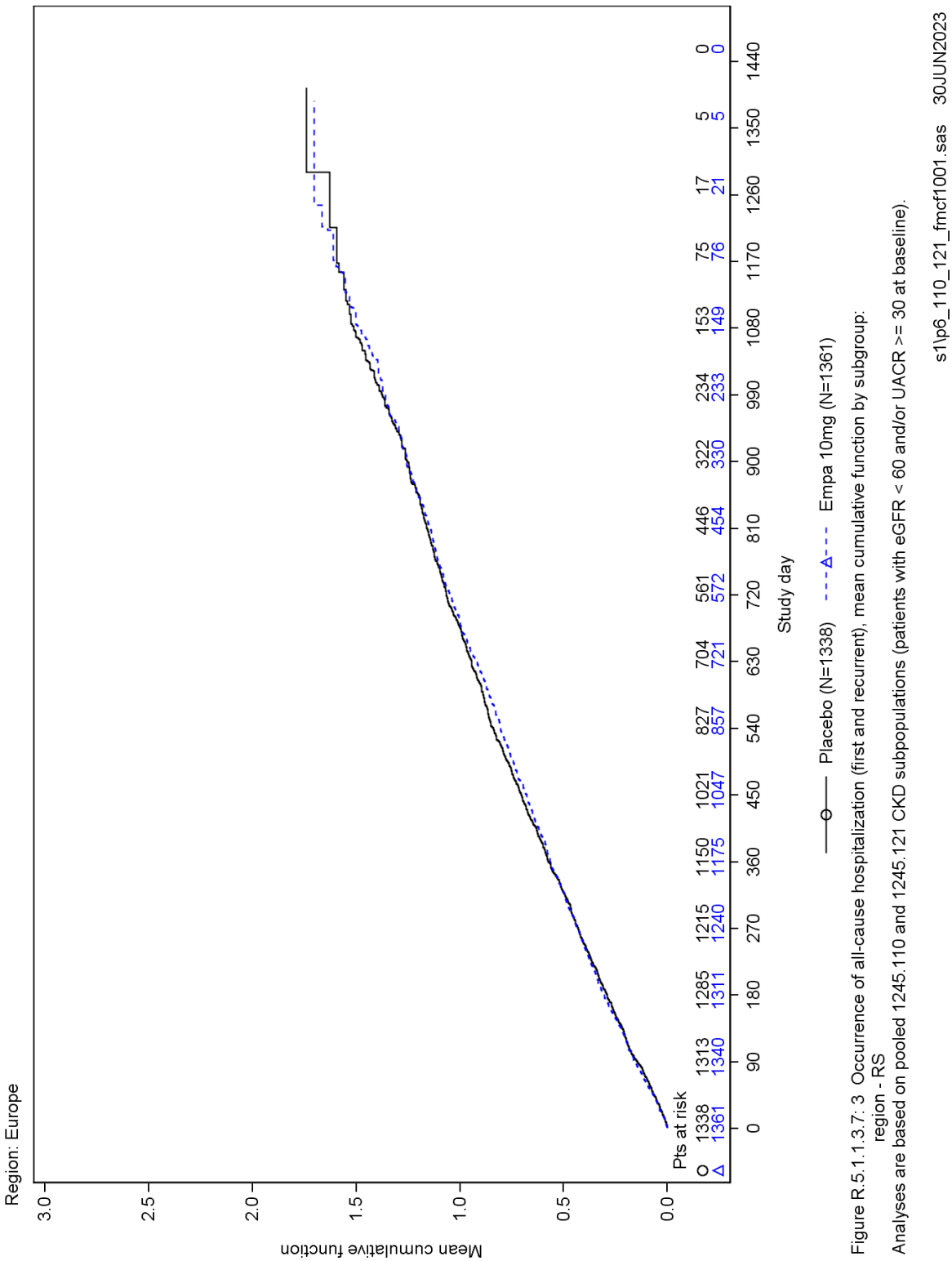


Figure R.5.1.1.3.7: 3 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: region - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**Figure R.5.1.1.3.7: 3**

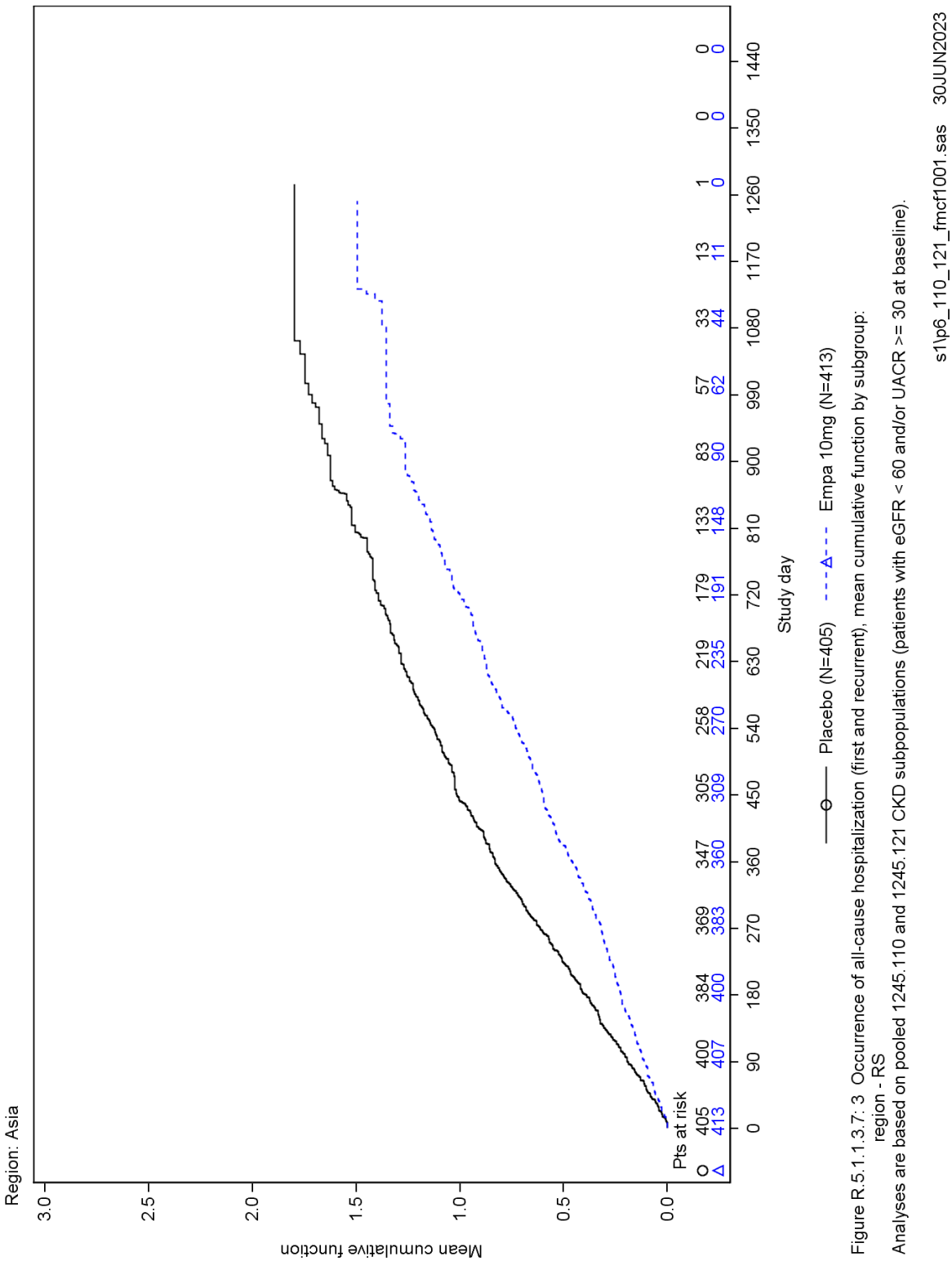


Figure R.5.1.1.3.7: 3 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: region - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**Figure R.5.1.1.3.7: 3**

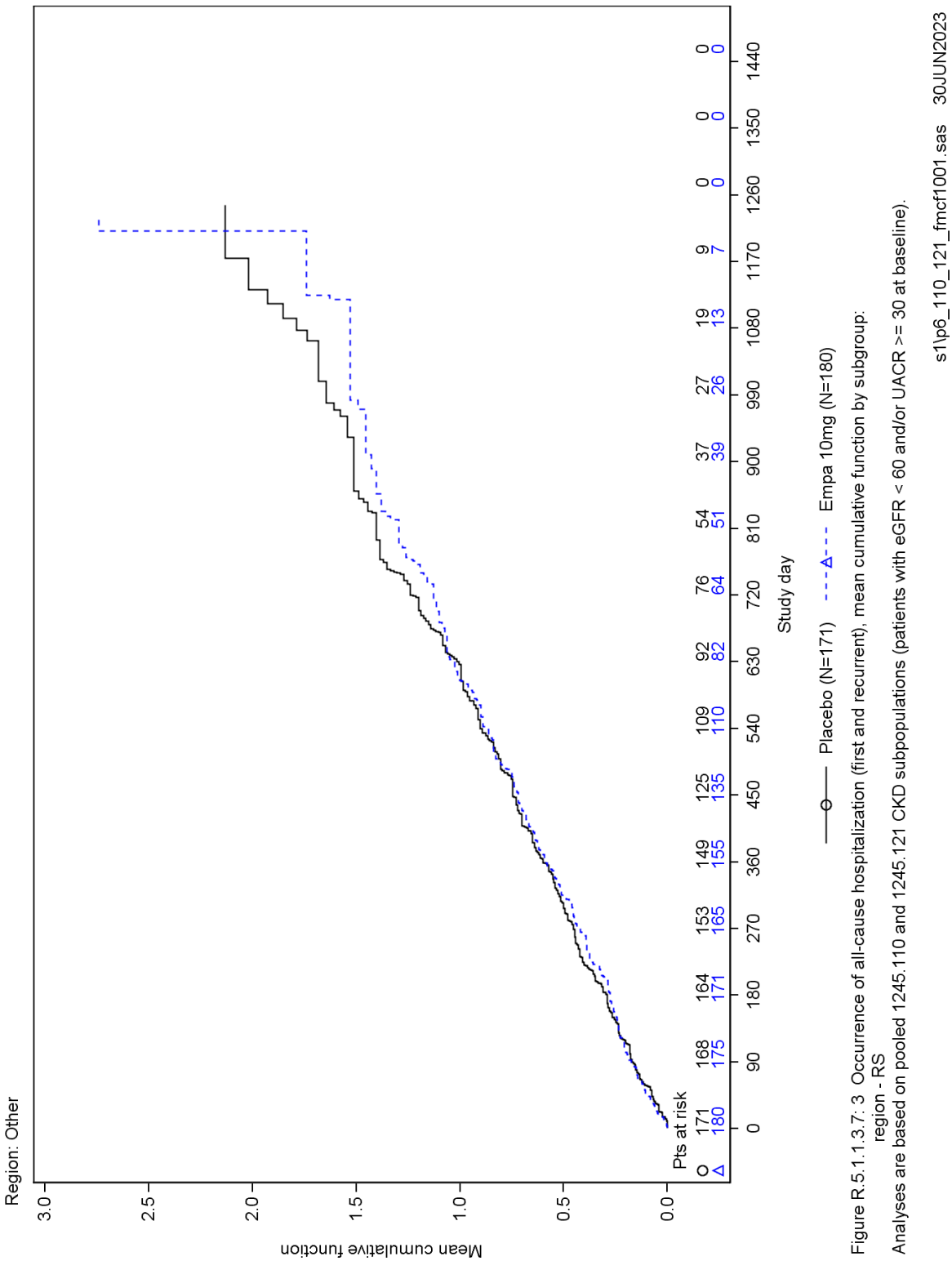


Figure R.5.1.1.3.7: 3 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: region - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**Figure R.5.1.1.3.7: 4**

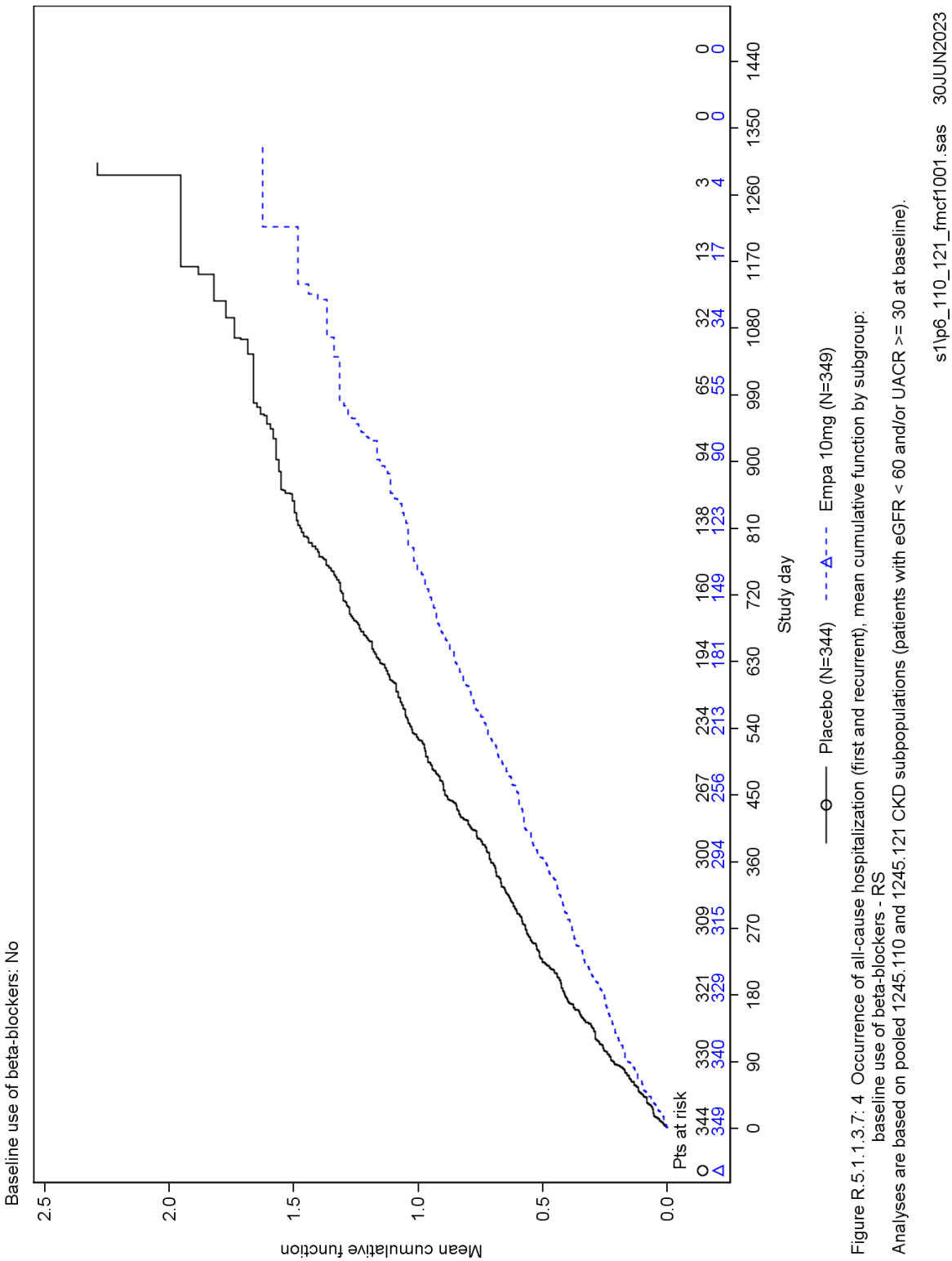


Figure R.5.1.1.3.7: 4 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: baseline use of beta-blockers - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**Figure R.5.1.1.3.7: 4**

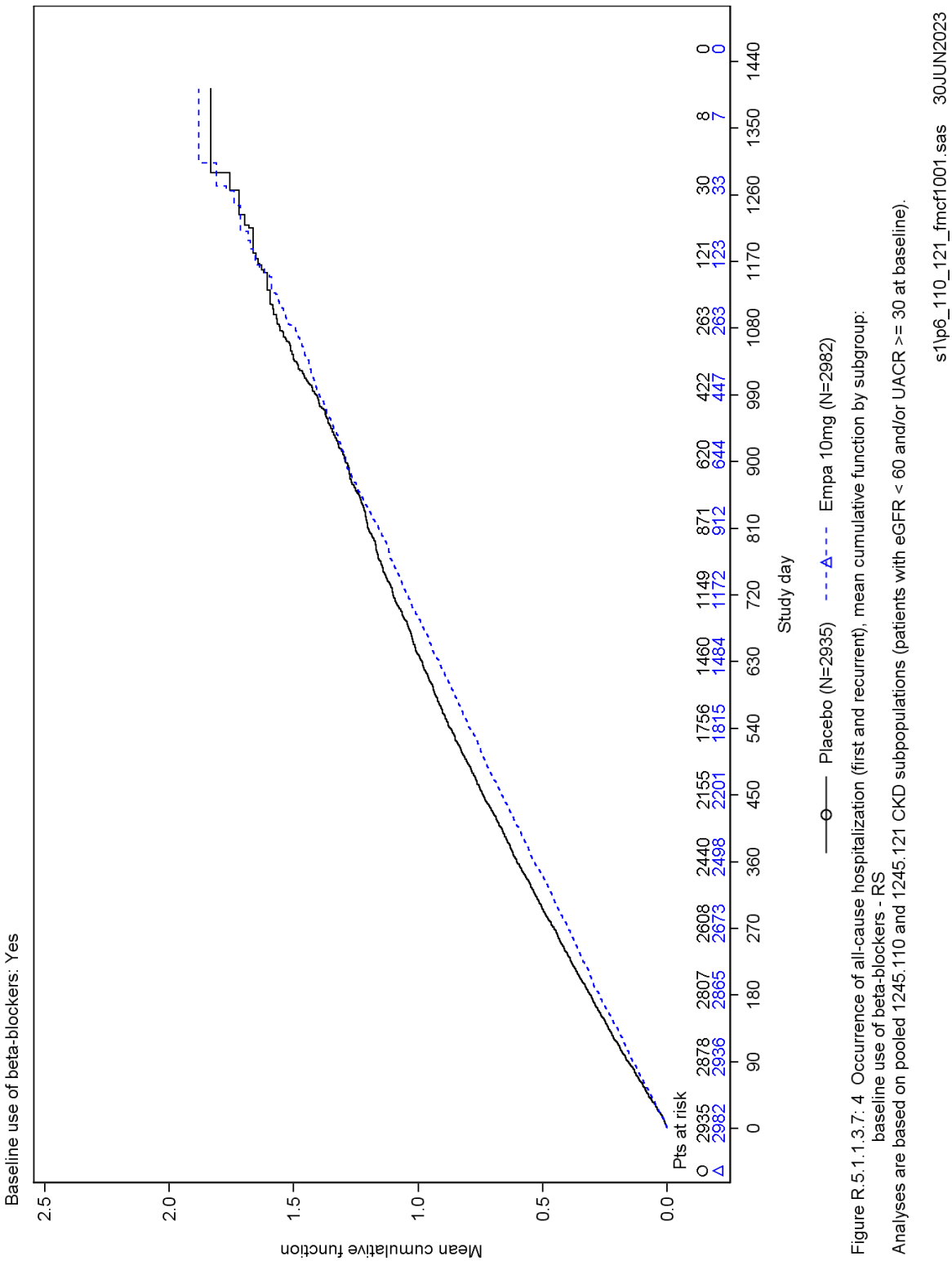


Figure R.5.1.1.3.7: 4 Occurrence of all-cause hospitalization (first and recurrent), mean cumulative function by subgroup: baseline use of beta-blockers - RS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

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**R.5.1.2**

R.5.1.2.1 Responder analyses based on last value during planned treatment period

**R.5.1.2.1.1**

R.5.1.2.1.1 EQ-VAS responder analysis (15 points)

**Figure R.5.1.2.1.1: 1**

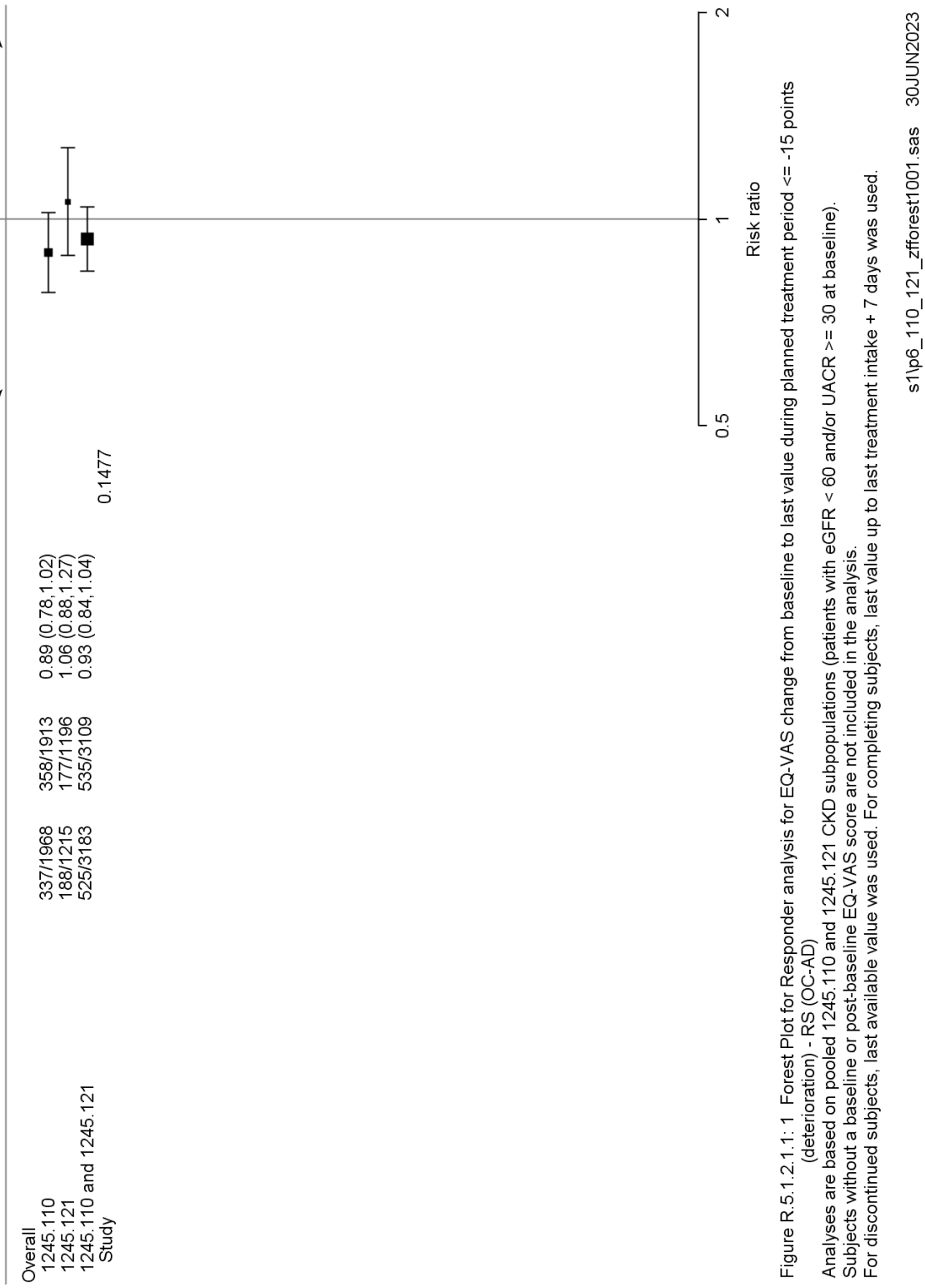


Figure R.5.1.2.1.1: 1 Forest Plot for Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -15 points (deterioration) - RS (OC-AD)
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3109 | 535 | 17.2 | 3183 | 525 | 16.5 | 0.93 | (0.84,1.04) | 0.2183 | 0.95 | (0.83,1.09) | |
| Study | | | | | | | | | | | | 0.1477 |
| Sex | | | | | | | | | | | | 0.9425 |
| Male | 1926 | 325 | 16.9 | 1981 | 324 | 16.4 | 0.93 | (0.81,1.07) | 0.3182 | 0.99 | (0.83,1.17) | |
| Female | 1183 | 210 | 17.8 | 1202 | 201 | 16.7 | 0.94 | (0.79,1.11) | 0.4704 | 0.90 | (0.72,1.12) | |
| Age [years] | | | | | | | | | | | | 0.3087 |
| <65 | 724 | 92 | 12.7 | 677 | 84 | 12.4 | 0.81 | (0.60,1.09) | 0.1629 | 1.01 | (0.72,1.40) | |
| >=65 | 2385 | 443 | 18.6 | 2506 | 441 | 17.6 | 0.95 | (0.85,1.07) | 0.4374 | 0.94 | (0.81,1.09) | |
| Region | | | | | | | | | | | | 0.1503 |
| North America | 407 | 72 | 17.7 | 414 | 88 | 21.3 | 1.17 | (0.89,1.55) | 0.2501 | 1.24 | (0.87,1.78) | |
| Latin America | 873 | 114 | 13.1 | 888 | 121 | 13.6 | 0.92 | (0.72,1.18) | 0.5280 | 1.07 | (0.80,1.42) | |
| Europe | 1283 | 255 | 19.9 | 1314 | 238 | 18.1 | 0.91 | (0.78,1.06) | 0.2423 | 0.87 | (0.71,1.07) | |
| Asia | 393 | 67 | 17.0 | 401 | 64 | 16.0 | 0.95 | (0.70,1.29) | 0.7303 | 0.98 | (0.66,1.44) | |
| Other | 153 | 27 | 17.6 | 166 | 14 | 8.4 | 0.51 | (0.28,0.93) | 0.0268 | 0.46 | (0.23,0.93) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.1255 |
| Diabetic | 1648 | 279 | 16.9 | 1694 | 287 | 16.9 | 1.01 | (0.87,1.17) | 0.9034 | 1.03 | (0.85,1.24) | |
| Non-Diabetic | 1461 | 256 | 17.5 | 1489 | 238 | 16.0 | 0.85 | (0.72,1.00) | 0.0505 | 0.87 | (0.71,1.07) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.3841 |
| <30 | 1872 | 308 | 16.5 | 1843 | 298 | 16.2 | 0.97 | (0.84,1.12) | 0.6914 | 0.95 | (0.80,1.14) | |
| >=30 | 1237 | 227 | 18.4 | 1340 | 227 | 16.9 | 0.88 | (0.74,1.04) | 0.1407 | 0.94 | (0.76,1.16) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.8831 |
| <130 | 1592 | 270 | 17.0 | 1605 | 259 | 16.1 | 0.94 | (0.81,1.10) | 0.4383 | 0.94 | (0.77,1.14) | |
| >=130 | 1517 | 265 | 17.5 | 1578 | 266 | 16.9 | 0.93 | (0.79,1.08) | 0.3356 | 0.97 | (0.79,1.17) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5287 |
| <75 | 1576 | 298 | 18.9 | 1536 | 286 | 18.6 | 0.99 | (0.86,1.14) | 0.9111 | 1.00 | (0.83,1.21) | |
| 75 to <85 | 943 | 156 | 16.5 | 1038 | 153 | 14.7 | 0.88 | (0.72,1.08) | 0.2286 | 0.85 | (0.66,1.10) | |
| >=85 | 590 | 81 | 13.7 | 609 | 86 | 14.1 | 0.86 | (0.63,1.16) | 0.3123 | 1.02 | (0.73,1.43) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.4986 |
| <30 | 229 | 44 | 19.2 | 246 | 46 | 18.7 | 1.01 | (0.70,1.46) | 0.9600 | 1.10 | (0.68,1.78) | |
| 30 to <45 | 866 | 161 | 18.6 | 875 | 165 | 18.9 | 1.01 | (0.84,1.22) | 0.9129 | 0.97 | (0.75,1.25) | |
| >=45 | 2013 | 330 | 16.4 | 2062 | 314 | 15.2 | 0.88 | (0.77,1.02) | 0.0905 | 0.92 | (0.77,1.10) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7339 |
| Normal (<30) | 1169 | 226 | 19.3 | 1204 | 225 | 18.7 | 0.98 | (0.84,1.16) | 0.8314 | 0.97 | (0.78,1.20) | |
| Microalbuminuria (30 to <=300) | 1452 | 237 | 16.3 | 1460 | 229 | 15.7 | 0.89 | (0.76,1.06) | 0.1942 | 0.95 | (0.77,1.17) | |
| Macroalbuminuria (>300) | 479 | 70 | 14.6 | 504 | 69 | 13.7 | 0.93 | (0.69,1.25) | 0.6319 | 0.92 | (0.63,1.34) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.7245 |
| Low, moderate or high | 2306 | 388 | 16.8 | 2393 | 388 | 16.2 | 0.93 | (0.81,1.05) | 0.2392 | 0.95 | (0.81,1.12) | |
| Very high | 794 | 145 | 18.3 | 776 | 136 | 17.5 | 0.97 | (0.79,1.19) | 0.7548 | 0.97 | (0.74,1.27) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.3197 |
| No | 540 | 105 | 19.4 | 550 | 90 | 16.4 | 0.83 | (0.65,1.07) | 0.1504 | 0.78 | (0.57,1.08) | |
| Yes | 2569 | 430 | 16.7 | 2633 | 435 | 16.5 | 0.96 | (0.85,1.08) | 0.4940 | 0.99 | (0.85,1.16) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.5919 |
| No | 318 | 60 | 18.9 | 324 | 62 | 19.1 | 1.01 | (0.74,1.38) | 0.9398 | 0.99 | (0.66,1.50) | |
| Yes | 2791 | 475 | 17.0 | 2859 | 463 | 16.2 | 0.92 | (0.82,1.04) | 0.1831 | 0.95 | (0.82,1.09) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.1: 1 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | | 0.0384 |
| No | 262 | 52 | 19.8 | 291 | 37 | 12.7 | 0.64 | (0.44,0.93) | 0.0198 | 0.58 | (0.36,0.93) | |
| Yes | 2847 | 483 | 17.0 | 2892 | 488 | 16.9 | 0.97 | (0.86,1.08) | 0.5727 | 1.00 | (0.86,1.15) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**Figure R.5.1.2.1.1: 2**

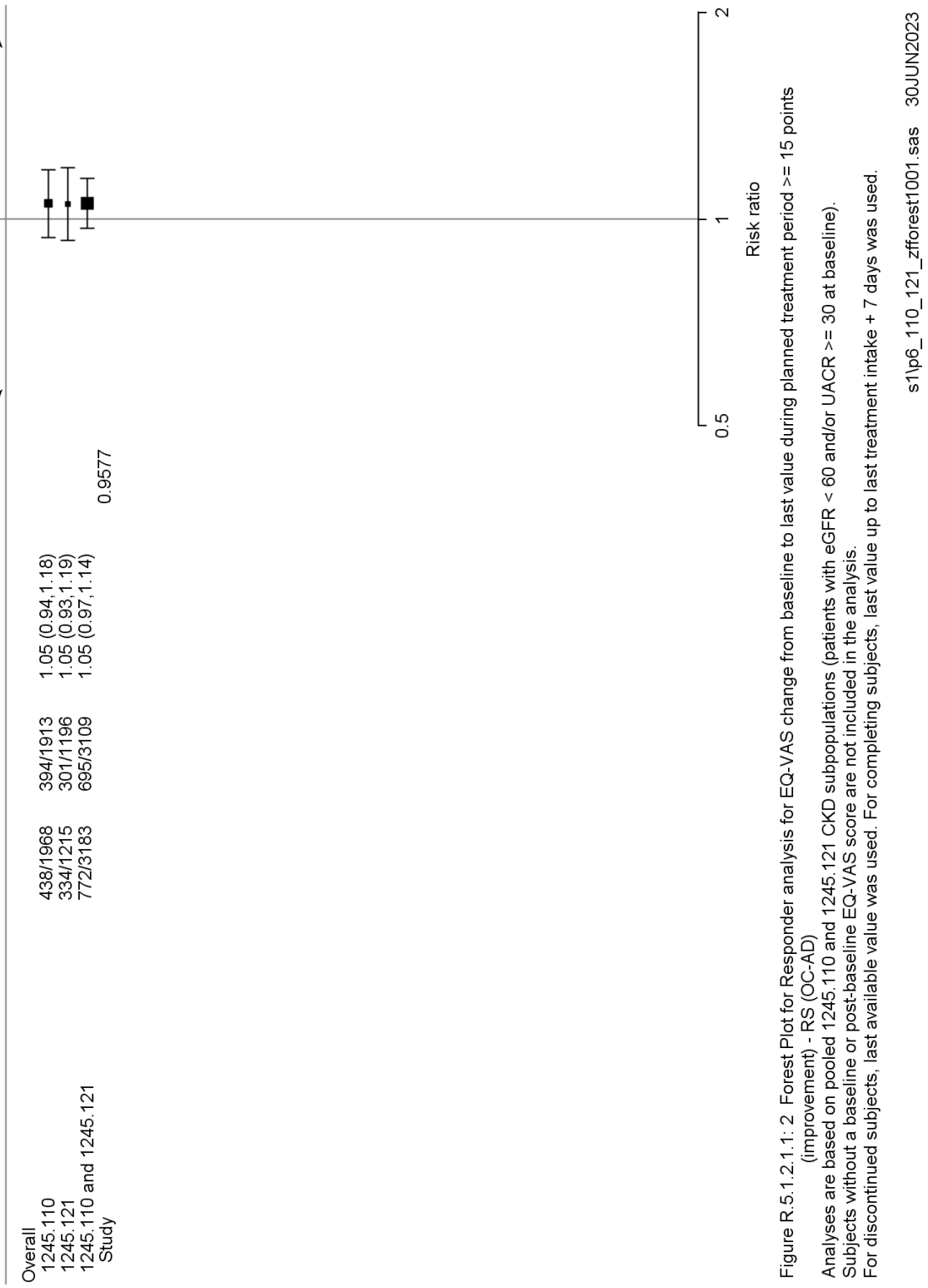


Figure R.5.1.2.1.1: 2 Forest Plot for Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 15 points (improvement) - RS (OC-AD)
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3109 | 695 | 22.4 | 3183 | 772 | 24.3 | 1.05 | (0.97,1.14) | 0.2276 | 1.12 | (0.98,1.28) | |
| Study | | | | | | | | | | | | 0.9577 |
| Sex | | | | | | | | | | | | 0.8614 |
| Male | 1926 | 423 | 22.0 | 1981 | 469 | 23.7 | 1.05 | (0.94,1.16) | 0.4067 | 1.08 | (0.91,1.29) | |
| Female | 1183 | 272 | 23.0 | 1202 | 303 | 25.2 | 1.06 | (0.93,1.21) | 0.3712 | 1.18 | (0.95,1.47) | |
| Age [years] | | | | | | | | | | | | 0.2229 |
| <65 | 724 | 190 | 26.2 | 677 | 216 | 31.9 | 1.14 | (0.98,1.33) | 0.0900 | 1.32 | (1.00,1.74) | |
| >=65 | 2385 | 505 | 21.2 | 2506 | 556 | 22.2 | 1.02 | (0.92,1.13) | 0.7006 | 1.06 | (0.91,1.24) | |
| Region | | | | | | | | | | | | 0.9559 |
| North America | 407 | 81 | 19.9 | 414 | 88 | 21.3 | 1.06 | (0.82,1.36) | 0.6465 | 1.17 | (0.79,1.73) | |
| Latin America | 873 | 263 | 30.1 | 888 | 295 | 33.2 | 1.08 | (0.95,1.23) | 0.2632 | 1.20 | (0.95,1.52) | |
| Europe | 1283 | 242 | 18.9 | 1314 | 261 | 19.9 | 1.06 | (0.91,1.23) | 0.4596 | 1.10 | (0.89,1.38) | |
| Asia | 393 | 71 | 18.1 | 401 | 79 | 19.7 | 1.00 | (0.77,1.28) | 0.9808 | 0.97 | (0.65,1.45) | |
| Other | 153 | 38 | 24.8 | 166 | 49 | 29.5 | 0.95 | (0.69,1.32) | 0.7742 | 0.97 | (0.55,1.72) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.0303 |
| Diabetic | 1648 | 389 | 23.6 | 1694 | 468 | 27.6 | 1.14 | (1.02,1.27) | 0.0200 | 1.29 | (1.08,1.55) | |
| Non-Diabetic | 1461 | 306 | 20.9 | 1489 | 304 | 20.4 | 0.94 | (0.83,1.07) | 0.3847 | 0.93 | (0.76,1.15) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.1901 |
| <30 | 1872 | 422 | 22.5 | 1843 | 403 | 21.9 | 1.00 | (0.90,1.12) | 0.9389 | 1.01 | (0.85,1.21) | |
| >=30 | 1237 | 273 | 22.1 | 1340 | 369 | 27.5 | 1.12 | (0.99,1.28) | 0.0705 | 1.29 | (1.05,1.59) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.6097 |
| <130 | 1592 | 361 | 22.7 | 1605 | 397 | 24.7 | 1.07 | (0.96,1.21) | 0.2201 | 1.13 | (0.94,1.37) | |
| >=130 | 1517 | 334 | 22.0 | 1578 | 375 | 23.8 | 1.03 | (0.91,1.16) | 0.6428 | 1.10 | (0.91,1.34) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7968 |
| <75 | 1576 | 341 | 21.6 | 1536 | 362 | 23.6 | 1.02 | (0.90,1.16) | 0.7259 | 1.05 | (0.87,1.28) | |
| 75 to <85 | 943 | 216 | 22.9 | 1038 | 252 | 24.3 | 1.07 | (0.93,1.24) | 0.3282 | 1.17 | (0.92,1.49) | |
| >=85 | 590 | 138 | 23.4 | 609 | 158 | 25.9 | 1.09 | (0.91,1.32) | 0.3494 | 1.21 | (0.89,1.65) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.0745 |
| <30 | 229 | 39 | 17.0 | 246 | 70 | 28.5 | 1.49 | (1.08,2.05) | 0.0159 | 1.97 | (1.19,3.29) | |
| 30 to <45 | 866 | 197 | 22.7 | 875 | 200 | 22.9 | 0.98 | (0.83,1.15) | 0.7943 | 1.03 | (0.79,1.33) | |
| >=45 | 2013 | 459 | 22.8 | 2062 | 502 | 24.3 | 1.05 | (0.95,1.16) | 0.3769 | 1.09 | (0.92,1.29) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.3252 |
| Normal (<30) | 1169 | 238 | 20.4 | 1204 | 257 | 21.3 | 1.03 | (0.88,1.19) | 0.7399 | 1.08 | (0.86,1.36) | |
| Microalbuminuria (30 to <=300) | 1452 | 329 | 22.7 | 1460 | 354 | 24.2 | 1.02 | (0.90,1.15) | 0.7897 | 1.06 | (0.87,1.29) | |
| Macroalbuminuria (>300) | 479 | 125 | 26.1 | 504 | 155 | 30.8 | 1.19 | (0.99,1.43) | 0.0580 | 1.38 | (1.00,1.92) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4190 |
| Low, moderate or high | 2306 | 510 | 22.1 | 2393 | 562 | 23.5 | 1.03 | (0.93,1.14) | 0.5513 | 1.09 | (0.93,1.27) | |
| Very high | 794 | 182 | 22.9 | 776 | 204 | 26.3 | 1.11 | (0.95,1.30) | 0.1840 | 1.21 | (0.93,1.58) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6864 |
| No | 540 | 115 | 21.3 | 550 | 131 | 23.8 | 1.09 | (0.89,1.34) | 0.3931 | 1.20 | (0.86,1.67) | |
| Yes | 2569 | 580 | 22.6 | 2633 | 641 | 24.3 | 1.04 | (0.95,1.14) | 0.3539 | 1.10 | (0.95,1.28) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4974 |
| No | 318 | 67 | 21.1 | 324 | 68 | 21.0 | 0.96 | (0.72,1.28) | 0.7674 | 0.93 | (0.61,1.44) | |
| Yes | 2791 | 628 | 22.5 | 2859 | 704 | 24.6 | 1.06 | (0.97,1.16) | 0.1701 | 1.14 | (0.99,1.32) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.1: 2 Responder analysis for EQ-VAS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | | 0.2349 |
| No | 262 | 56 | 21.4 | 291 | 60 | 20.6 | 0.89 | (0.67,1.18) | 0.4248 | 0.90 | (0.56,1.43) | |
| Yes | 2847 | 639 | 22.4 | 2892 | 712 | 24.6 | 1.07 | (0.98,1.16) | 0.1452 | 1.14 | (0.99,1.32) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline EQ-VAS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline EQ-VAS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**R.5.1.2.1.2**

R.5.1.2.1.2 KCCQ-OSS responder analysis (5 points)

**Figure R.5.1.2.1.2: 1**

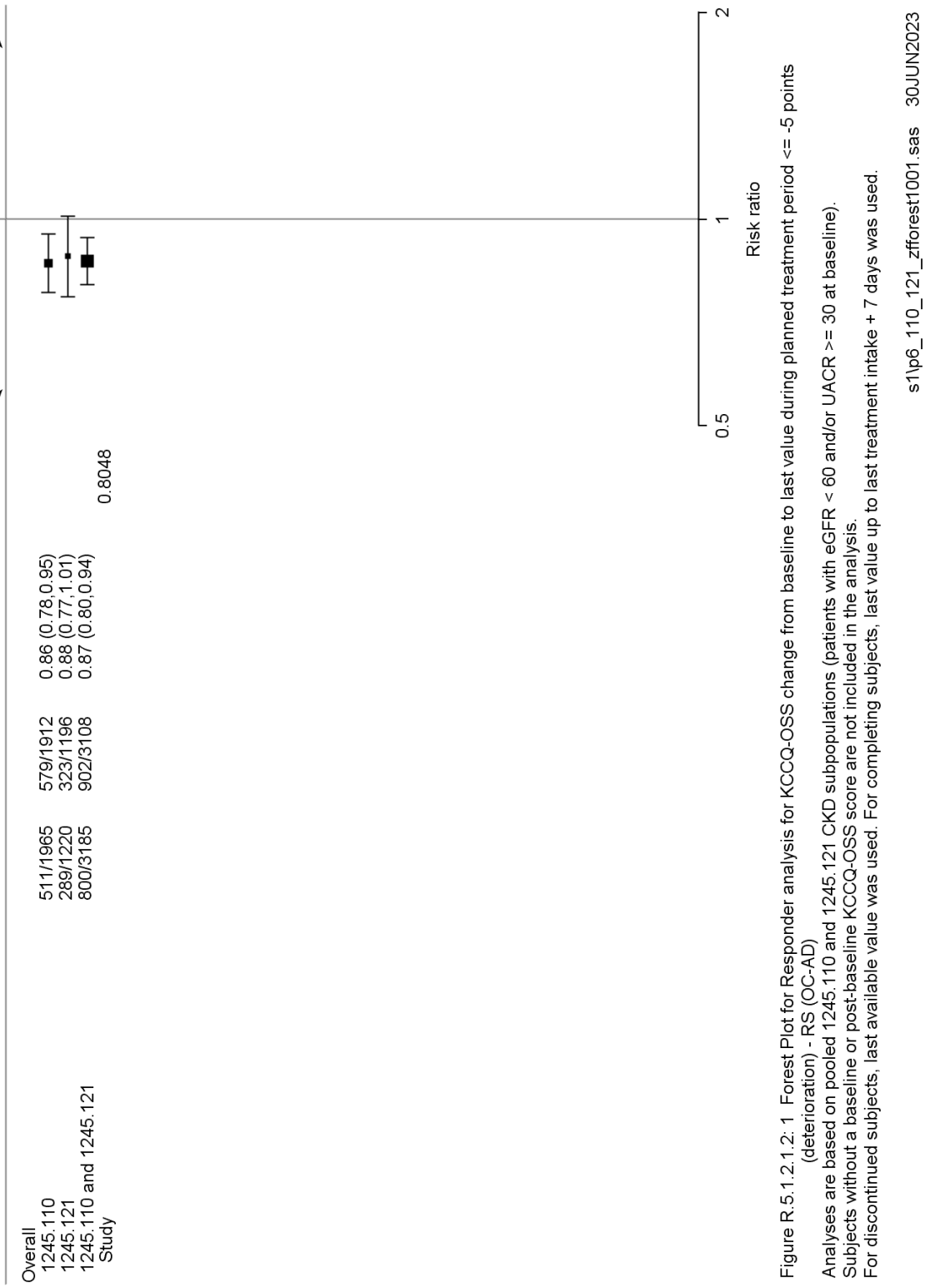


Figure R.5.1.2.1.2: 1 Forest Plot for Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -5 points (deterioration) - RS (OC-AD)

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.2: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -5 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3108 | 902 | 29.0 | 3185 | 800 | 25.1 | 0.87 | (0.80,0.94) | 0.0005 | 0.82 | (0.73,0.91) | |
| Study | | | | | | | | | | | | 0.8048 |
| Sex | | | | | | | | | | | | 0.8430 |
| Male | 1925 | 579 | 30.1 | 1980 | 510 | 25.8 | 0.86 | (0.78,0.95) | 0.0034 | 0.81 | (0.70,0.93) | |
| Female | 1183 | 323 | 27.3 | 1205 | 290 | 24.1 | 0.88 | (0.77,1.00) | 0.0526 | 0.83 | (0.69,1.01) | |
| Age [years] | | | | | | | | | | | | 0.7876 |
| <65 | 725 | 169 | 23.3 | 677 | 143 | 21.1 | 0.89 | (0.73,1.08) | 0.2285 | 0.85 | (0.66,1.10) | |
| >=65 | 2383 | 733 | 30.8 | 2508 | 657 | 26.2 | 0.86 | (0.79,0.94) | 0.0008 | 0.81 | (0.71,0.92) | |
| Region | | | | | | | | | | | | 0.5090 |
| North America | 408 | 107 | 26.2 | 415 | 107 | 25.8 | 0.97 | (0.77,1.21) | 0.7640 | 0.95 | (0.69,1.31) | |
| Latin America | 874 | 207 | 23.7 | 888 | 178 | 20.0 | 0.85 | (0.72,1.01) | 0.0724 | 0.81 | (0.64,1.02) | |
| Europe | 1283 | 413 | 32.2 | 1318 | 381 | 28.9 | 0.90 | (0.80,1.00) | 0.0574 | 0.85 | (0.72,1.01) | |
| Asia | 390 | 130 | 33.3 | 399 | 97 | 24.3 | 0.74 | (0.60,0.93) | 0.0083 | 0.65 | (0.48,0.89) | |
| Other | 153 | 45 | 29.4 | 165 | 37 | 22.4 | 0.79 | (0.55,1.14) | 0.2059 | 0.72 | (0.43,1.21) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.5991 |
| Diabetic | 1646 | 468 | 28.4 | 1694 | 412 | 24.3 | 0.85 | (0.76,0.95) | 0.0042 | 0.80 | (0.68,0.93) | |
| Non-Diabetic | 1462 | 434 | 29.7 | 1491 | 388 | 26.0 | 0.89 | (0.79,0.99) | 0.0404 | 0.84 | (0.71,0.99) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.9038 |
| <30 | 1868 | 534 | 28.6 | 1843 | 461 | 25.0 | 0.87 | (0.78,0.97) | 0.0086 | 0.82 | (0.71,0.95) | |
| >=30 | 1240 | 368 | 29.7 | 1342 | 339 | 25.3 | 0.86 | (0.76,0.97) | 0.0169 | 0.81 | (0.67,0.96) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.0532 |
| <130 | 1591 | 432 | 27.2 | 1609 | 414 | 25.7 | 0.94 | (0.84,1.05) | 0.2728 | 0.91 | (0.78,1.07) | |
| >=130 | 1517 | 470 | 31.0 | 1576 | 386 | 24.5 | 0.80 | (0.72,0.90) | 0.0001 | 0.73 | (0.62,0.85) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.2: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -5 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5400 |
| <75 | 1574 | 460 | 29.2 | 1541 | 405 | 26.3 | 0.91 | (0.81,1.01) | 0.0843 | 0.87 | (0.74,1.02) | |
| 75 to <85 | 945 | 272 | 28.8 | 1036 | 251 | 24.2 | 0.82 | (0.71,0.95) | 0.0080 | 0.76 | (0.62,0.93) | |
| >=85 | 589 | 170 | 28.9 | 608 | 144 | 23.7 | 0.84 | (0.70,1.01) | 0.0697 | 0.78 | (0.60,1.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.1623 |
| <30 | 230 | 81 | 35.2 | 246 | 58 | 23.6 | 0.67 | (0.51,0.88) | 0.0046 | 0.56 | (0.37,0.84) | |
| 30 to <45 | 866 | 278 | 32.1 | 875 | 251 | 28.7 | 0.90 | (0.78,1.03) | 0.1338 | 0.85 | (0.69,1.05) | |
| >=45 | 2011 | 543 | 27.0 | 2064 | 491 | 23.8 | 0.88 | (0.79,0.98) | 0.0159 | 0.84 | (0.72,0.97) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.0874 |
| Normal (<30) | 1168 | 338 | 28.9 | 1203 | 332 | 27.6 | 0.96 | (0.85,1.09) | 0.5650 | 0.95 | (0.79,1.14) | |
| Microalbuminuria (30 to <=300) | 1453 | 423 | 29.1 | 1462 | 349 | 23.9 | 0.82 | (0.73,0.93) | 0.0014 | 0.76 | (0.64,0.90) | |
| Macroalbuminuria (>300) | 478 | 139 | 29.1 | 505 | 115 | 22.8 | 0.76 | (0.62,0.94) | 0.0099 | 0.68 | (0.50,0.91) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3625 |
| Low, moderate or high | 2305 | 636 | 27.6 | 2394 | 586 | 24.5 | 0.89 | (0.81,0.98) | 0.0141 | 0.85 | (0.74,0.97) | |
| Very high | 794 | 264 | 33.2 | 777 | 210 | 27.0 | 0.82 | (0.71,0.95) | 0.0074 | 0.74 | (0.59,0.92) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5453 |
| No | 541 | 172 | 31.8 | 547 | 146 | 26.7 | 0.82 | (0.69,0.99) | 0.0358 | 0.75 | (0.58,0.99) | |
| Yes | 2567 | 730 | 28.4 | 2638 | 654 | 24.8 | 0.88 | (0.80,0.96) | 0.0038 | 0.83 | (0.73,0.94) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.2731 |
| No | 317 | 101 | 31.9 | 324 | 78 | 24.1 | 0.76 | (0.60,0.97) | 0.0292 | 0.68 | (0.47,0.97) | |
| Yes | 2791 | 801 | 28.7 | 2861 | 722 | 25.2 | 0.88 | (0.81,0.96) | 0.0030 | 0.83 | (0.74,0.94) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.2: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -5 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | | 0.6067 |
| No | 261 | 68 | 26.1 | 291 | 62 | 21.3 | 0.81 | (0.60,1.08) | 0.1534 | 0.75 | (0.50,1.12) | |
| Yes | 2847 | 834 | 29.3 | 2894 | 738 | 25.5 | 0.87 | (0.81,0.95) | 0.0015 | 0.82 | (0.73,0.93) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**Figure R.5.1.2.1.2: 2**

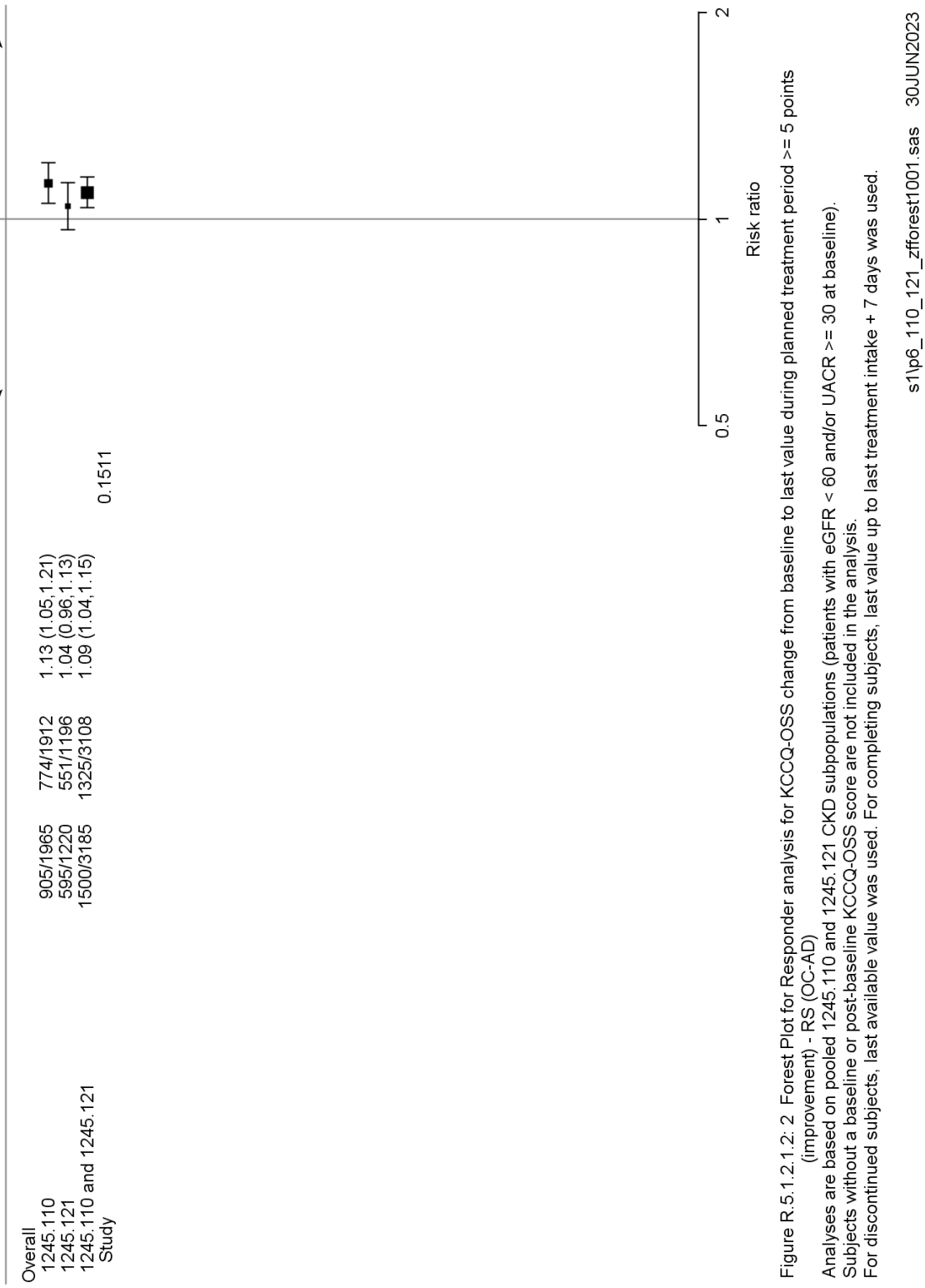


Figure R.5.1.2.1.2: 2 Forest Plot for Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 5 points (improvement) - RS (OC-AD)
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.2: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 5 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3108 | 1325 | 42.6 | 3185 | 1500 | 47.1 | 1.09 | (1.04,1.15) | 0.0008 | 1.22 | (1.09,1.36) | |
| Study | | | | | | | | | | | | 0.1511 |
| Sex | | | | | | | | | | | | 0.7760 |
| Male | 1925 | 782 | 40.6 | 1980 | 896 | 45.3 | 1.10 | (1.03,1.18) | 0.0067 | 1.22 | (1.06,1.40) | |
| Female | 1183 | 543 | 45.9 | 1205 | 604 | 50.1 | 1.08 | (1.00,1.17) | 0.0504 | 1.22 | (1.03,1.46) | |
| Age [years] | | | | | | | | | | | | 0.0452 |
| <65 | 725 | 376 | 51.9 | 677 | 353 | 52.1 | 1.00 | (0.91,1.10) | 0.9949 | 1.03 | (0.82,1.30) | |
| >=65 | 2383 | 949 | 39.8 | 2508 | 1147 | 45.7 | 1.12 | (1.06,1.19) | 0.0002 | 1.28 | (1.13,1.44) | |
| Region | | | | | | | | | | | | 0.6241 |
| North America | 408 | 164 | 40.2 | 415 | 183 | 44.1 | 1.12 | (0.96,1.30) | 0.1479 | 1.26 | (0.94,1.71) | |
| Latin America | 874 | 470 | 53.8 | 888 | 515 | 58.0 | 1.07 | (0.98,1.15) | 0.1166 | 1.20 | (0.98,1.48) | |
| Europe | 1283 | 494 | 38.5 | 1318 | 558 | 42.3 | 1.09 | (1.00,1.19) | 0.0496 | 1.20 | (1.01,1.42) | |
| Asia | 390 | 122 | 31.3 | 399 | 159 | 39.8 | 1.21 | (1.01,1.45) | 0.0338 | 1.39 | (1.02,1.90) | |
| Other | 153 | 75 | 49.0 | 165 | 85 | 51.5 | 0.99 | (0.81,1.22) | 0.9461 | 1.02 | (0.63,1.63) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.9257 |
| Diabetic | 1646 | 728 | 44.2 | 1694 | 825 | 48.7 | 1.09 | (1.02,1.17) | 0.0104 | 1.24 | (1.07,1.44) | |
| Non-Diabetic | 1462 | 597 | 40.8 | 1491 | 675 | 45.3 | 1.09 | (1.01,1.18) | 0.0310 | 1.20 | (1.02,1.40) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.0300 |
| <30 | 1868 | 798 | 42.7 | 1843 | 818 | 44.4 | 1.04 | (0.97,1.11) | 0.2468 | 1.09 | (0.95,1.26) | |
| >=30 | 1240 | 527 | 42.5 | 1342 | 682 | 50.8 | 1.17 | (1.08,1.27) | 0.0001 | 1.44 | (1.21,1.70) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.2993 |
| <130 | 1591 | 702 | 44.1 | 1609 | 750 | 46.6 | 1.06 | (0.99,1.14) | 0.0916 | 1.15 | (0.99,1.34) | |
| >=130 | 1517 | 623 | 41.1 | 1576 | 750 | 47.6 | 1.12 | (1.04,1.21) | 0.0024 | 1.29 | (1.11,1.51) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.2: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 5 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.7955 |
| <75 | 1574 | 652 | 41.4 | 1541 | 718 | 46.6 | 1.11 | (1.03,1.19) | 0.0078 | 1.24 | (1.06,1.45) | |
| 75 to <85 | 945 | 418 | 44.2 | 1036 | 480 | 46.3 | 1.06 | (0.97,1.17) | 0.1798 | 1.17 | (0.96,1.41) | |
| >=85 | 589 | 255 | 43.3 | 608 | 302 | 49.7 | 1.10 | (0.98,1.24) | 0.0957 | 1.26 | (0.98,1.61) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.9630 |
| <30 | 230 | 97 | 42.2 | 246 | 119 | 48.4 | 1.11 | (0.93,1.33) | 0.2566 | 1.29 | (0.87,1.92) | |
| 30 to <45 | 866 | 350 | 40.4 | 875 | 389 | 44.5 | 1.08 | (0.98,1.20) | 0.1376 | 1.19 | (0.97,1.47) | |
| >=45 | 2011 | 878 | 43.7 | 2064 | 992 | 48.1 | 1.09 | (1.03,1.17) | 0.0051 | 1.22 | (1.07,1.40) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.8530 |
| Normal (<30) | 1168 | 480 | 41.1 | 1203 | 540 | 44.9 | 1.07 | (0.98,1.17) | 0.1073 | 1.16 | (0.97,1.38) | |
| Microalbuminuria (30 to <=300) | 1453 | 618 | 42.5 | 1462 | 703 | 48.1 | 1.11 | (1.03,1.20) | 0.0079 | 1.28 | (1.09,1.50) | |
| Macroalbuminuria (>300) | 478 | 222 | 46.4 | 505 | 248 | 49.1 | 1.08 | (0.96,1.22) | 0.2148 | 1.20 | (0.91,1.58) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3245 |
| Low, moderate or high | 2305 | 979 | 42.5 | 2394 | 1138 | 47.5 | 1.11 | (1.04,1.17) | 0.0009 | 1.25 | (1.11,1.42) | |
| Very high | 794 | 341 | 42.9 | 777 | 353 | 45.4 | 1.04 | (0.94,1.16) | 0.4323 | 1.11 | (0.89,1.38) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5363 |
| No | 541 | 224 | 41.4 | 547 | 257 | 47.0 | 1.13 | (1.00,1.29) | 0.0569 | 1.32 | (1.01,1.71) | |
| Yes | 2567 | 1101 | 42.9 | 2638 | 1243 | 47.1 | 1.08 | (1.02,1.15) | 0.0052 | 1.20 | (1.07,1.35) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.8237 |
| No | 317 | 130 | 41.0 | 324 | 148 | 45.7 | 1.07 | (0.91,1.27) | 0.4076 | 1.19 | (0.85,1.68) | |
| Yes | 2791 | 1195 | 42.8 | 2861 | 1352 | 47.3 | 1.09 | (1.04,1.15) | 0.0012 | 1.22 | (1.09,1.37) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.2: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 5 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | | 0.2687 |
| No | 261 | 104 | 39.8 | 291 | 137 | 47.1 | 1.20 | (1.00,1.44) | 0.0447 | 1.42 | (0.98,2.04) | |
| Yes | 2847 | 1221 | 42.9 | 2894 | 1363 | 47.1 | 1.08 | (1.02,1.14) | 0.0044 | 1.20 | (1.07,1.34) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**R.5.1.2.1.3**

R.5.1.2.1.3 KCCQ-OSS responder analysis (15 points)

**Figure R.5.1.2.1.3: 1**

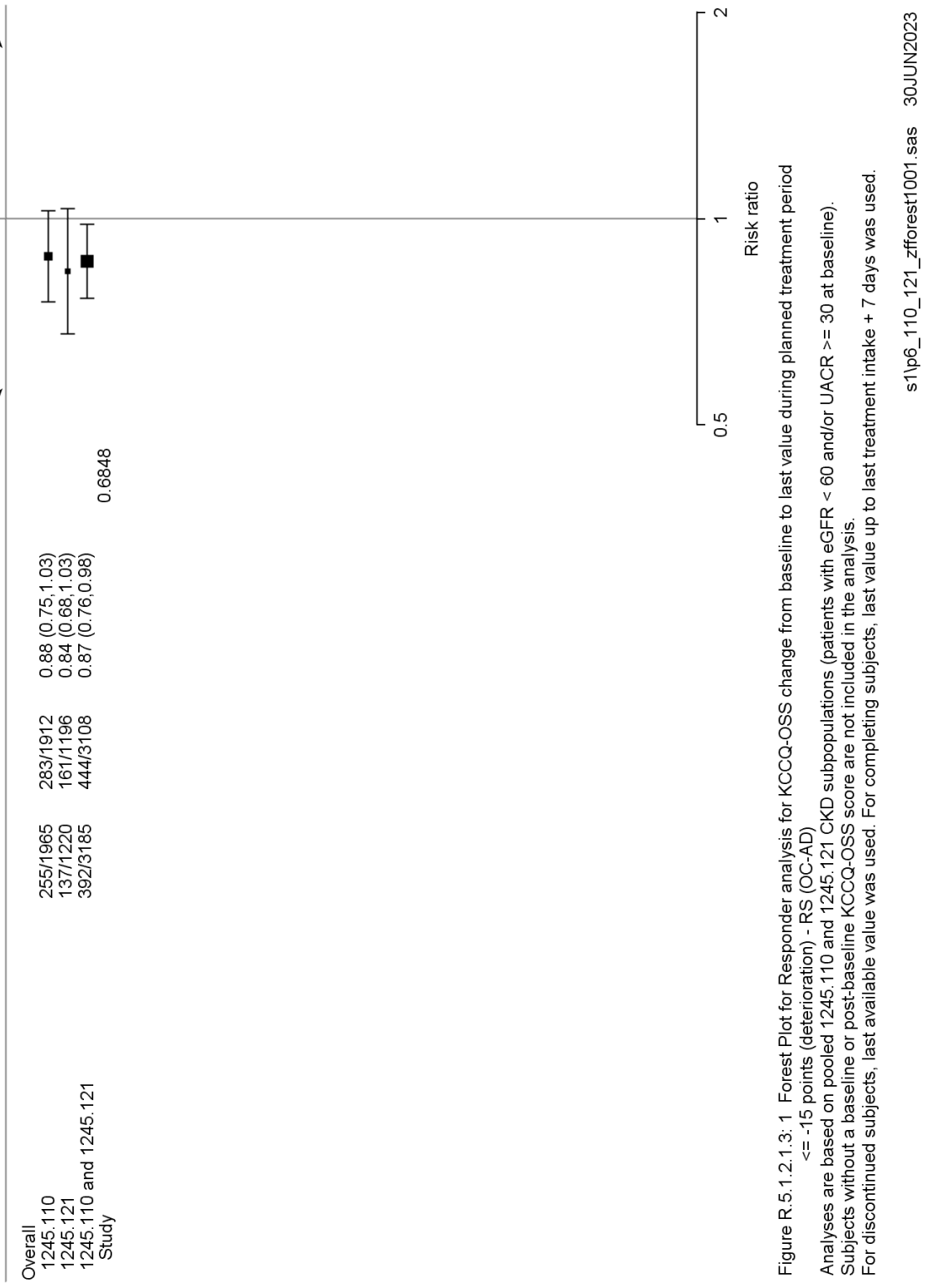


Figure R.5.1.2.1.3: 1 Forest Plot for Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period
<= -15 points (deterioration) - RS (OC-AD)
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.3: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3108 | 444 | 14.3 | 3185 | 392 | 12.3 | 0.87 | (0.76,0.98) | 0.0226 | 0.84 | (0.73,0.98) | |
| Study | | | | | | | | | | | | 0.6848 |
| Sex | | | | | | | | | | | | 0.2818 |
| Male | 1925 | 295 | 15.3 | 1980 | 247 | 12.5 | 0.82 | (0.70,0.96) | 0.0138 | 0.79 | (0.66,0.95) | |
| Female | 1183 | 149 | 12.6 | 1205 | 145 | 12.0 | 0.95 | (0.77,1.17) | 0.6254 | 0.94 | (0.74,1.21) | |
| Age [years] | | | | | | | | | | | | 0.6893 |
| <65 | 725 | 74 | 10.2 | 677 | 65 | 9.6 | 0.91 | (0.67,1.25) | 0.5738 | 0.90 | (0.63,1.29) | |
| >=65 | 2383 | 370 | 15.5 | 2508 | 327 | 13.0 | 0.85 | (0.74,0.98) | 0.0216 | 0.83 | (0.70,0.97) | |
| Region | | | | | | | | | | | | 0.1526 |
| North America | 408 | 55 | 13.5 | 415 | 54 | 13.0 | 0.94 | (0.67,1.33) | 0.7351 | 0.93 | (0.62,1.40) | |
| Latin America | 874 | 106 | 12.1 | 888 | 90 | 10.1 | 0.85 | (0.65,1.10) | 0.2119 | 0.82 | (0.61,1.12) | |
| Europe | 1283 | 187 | 14.6 | 1318 | 188 | 14.3 | 0.98 | (0.81,1.17) | 0.8036 | 0.97 | (0.78,1.21) | |
| Asia | 390 | 67 | 17.2 | 399 | 41 | 10.3 | 0.61 | (0.43,0.88) | 0.0078 | 0.56 | (0.37,0.85) | |
| Other | 153 | 29 | 19.0 | 165 | 19 | 11.5 | 0.64 | (0.38,1.08) | 0.0933 | 0.58 | (0.31,1.10) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.7296 |
| Diabetic | 1646 | 231 | 14.0 | 1694 | 203 | 12.0 | 0.85 | (0.71,1.01) | 0.0595 | 0.82 | (0.67,1.01) | |
| Non-Diabetic | 1462 | 213 | 14.6 | 1491 | 189 | 12.7 | 0.89 | (0.74,1.06) | 0.1832 | 0.86 | (0.70,1.07) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.7554 |
| <30 | 1868 | 263 | 14.1 | 1843 | 229 | 12.4 | 0.88 | (0.75,1.03) | 0.1177 | 0.86 | (0.71,1.04) | |
| >=30 | 1240 | 181 | 14.6 | 1342 | 163 | 12.1 | 0.84 | (0.70,1.02) | 0.0846 | 0.81 | (0.65,1.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.6523 |
| <130 | 1591 | 215 | 13.5 | 1609 | 196 | 12.2 | 0.89 | (0.75,1.06) | 0.2039 | 0.87 | (0.71,1.08) | |
| >=130 | 1517 | 229 | 15.1 | 1576 | 196 | 12.4 | 0.84 | (0.71,1.00) | 0.0516 | 0.81 | (0.66,1.00) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.3: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.5738 |
| <75 | 1574 | 235 | 14.9 | 1541 | 207 | 13.4 | 0.91 | (0.77,1.08) | 0.2698 | 0.89 | (0.73,1.09) | |
| 75 to <85 | 945 | 130 | 13.8 | 1036 | 115 | 11.1 | 0.78 | (0.62,0.99) | 0.0372 | 0.75 | (0.57,0.98) | |
| >=85 | 589 | 79 | 13.4 | 608 | 70 | 11.5 | 0.90 | (0.67,1.21) | 0.4854 | 0.88 | (0.62,1.25) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2389 |
| <30 | 230 | 48 | 20.9 | 246 | 32 | 13.0 | 0.64 | (0.43,0.95) | 0.0279 | 0.57 | (0.34,0.94) | |
| 30 to <45 | 866 | 144 | 16.6 | 875 | 120 | 13.7 | 0.84 | (0.67,1.04) | 0.1151 | 0.81 | (0.62,1.05) | |
| >=45 | 2011 | 252 | 12.5 | 2064 | 240 | 11.6 | 0.92 | (0.78,1.09) | 0.3318 | 0.91 | (0.75,1.10) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.5438 |
| Normal (<30) | 1168 | 169 | 14.5 | 1203 | 148 | 12.3 | 0.86 | (0.70,1.05) | 0.1464 | 0.84 | (0.66,1.06) | |
| Microalbuminuria (30 to <=300) | 1453 | 205 | 14.1 | 1462 | 185 | 12.7 | 0.91 | (0.76,1.09) | 0.2855 | 0.89 | (0.71,1.10) | |
| Macroalbuminuria (>300) | 478 | 70 | 14.6 | 505 | 56 | 11.1 | 0.74 | (0.54,1.01) | 0.0604 | 0.69 | (0.47,1.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.0907 |
| Low, moderate or high | 2305 | 296 | 12.8 | 2394 | 285 | 11.9 | 0.92 | (0.80,1.07) | 0.3084 | 0.91 | (0.76,1.09) | |
| Very high | 794 | 148 | 18.6 | 777 | 104 | 13.4 | 0.73 | (0.59,0.92) | 0.0065 | 0.68 | (0.51,0.90) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.0090 |
| No | 541 | 99 | 18.3 | 547 | 63 | 11.5 | 0.61 | (0.46,0.82) | 0.0008 | 0.55 | (0.39,0.78) | |
| Yes | 2567 | 345 | 13.4 | 2638 | 329 | 12.5 | 0.94 | (0.82,1.08) | 0.3623 | 0.93 | (0.79,1.09) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.1121 |
| No | 317 | 61 | 19.2 | 324 | 41 | 12.7 | 0.66 | (0.46,0.94) | 0.0217 | 0.60 | (0.39,0.93) | |
| Yes | 2791 | 383 | 13.7 | 2861 | 351 | 12.3 | 0.90 | (0.79,1.03) | 0.1123 | 0.88 | (0.75,1.03) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.3: 1 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period <= -15 points (deterioration) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | | 0.9061 |
| No | 261 | 37 | 14.2 | 291 | 35 | 12.0 | 0.85 | (0.55,1.30) | 0.4416 | 0.82 | (0.50,1.36) | |
| Yes | 2847 | 407 | 14.3 | 2894 | 357 | 12.3 | 0.87 | (0.76,0.99) | 0.0337 | 0.84 | (0.72,0.99) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**Figure R.5.1.2.1.3: 2**

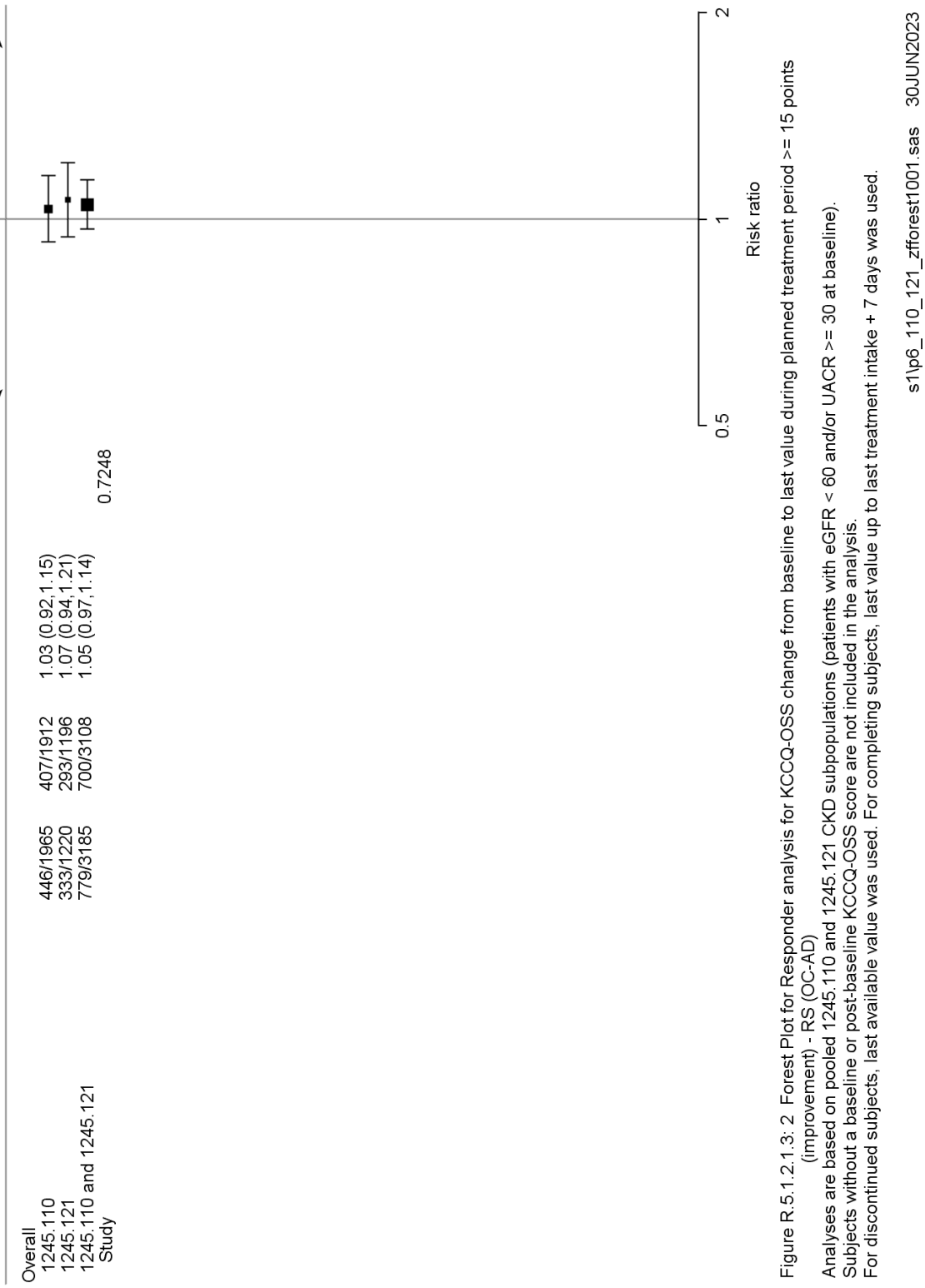


Figure R.5.1.2.1.3: 2 Forest Plot for Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 15 points (improvement) - RS (OC-AD)
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.3: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3108 | 700 | 22.5 | 3185 | 779 | 24.5 | 1.05 | (0.97,1.14) | 0.2595 | 1.10 | (0.97,1.26) | |
| Study | | | | | | | | | | | | 0.7248 |
| Sex | | | | | | | | | | | | 0.5904 |
| Male | 1925 | 403 | 20.9 | 1980 | 441 | 22.3 | 1.03 | (0.92,1.15) | 0.6178 | 1.05 | (0.89,1.25) | |
| Female | 1183 | 297 | 25.1 | 1205 | 338 | 28.0 | 1.08 | (0.95,1.22) | 0.2503 | 1.18 | (0.96,1.45) | |
| Age [years] | | | | | | | | | | | | 0.8960 |
| <65 | 725 | 206 | 28.4 | 677 | 208 | 30.7 | 1.05 | (0.90,1.23) | 0.5025 | 1.16 | (0.89,1.52) | |
| >=65 | 2383 | 494 | 20.7 | 2508 | 571 | 22.8 | 1.04 | (0.94,1.15) | 0.4109 | 1.08 | (0.93,1.26) | |
| Region | | | | | | | | | | | | 0.3142 |
| North America | 408 | 78 | 19.1 | 415 | 88 | 21.2 | 1.14 | (0.88,1.46) | 0.3211 | 1.24 | (0.85,1.81) | |
| Latin America | 874 | 293 | 33.5 | 888 | 329 | 37.0 | 1.07 | (0.95,1.21) | 0.2717 | 1.19 | (0.95,1.49) | |
| Europe | 1283 | 235 | 18.3 | 1318 | 237 | 18.0 | 0.96 | (0.82,1.12) | 0.5980 | 0.95 | (0.77,1.18) | |
| Asia | 390 | 53 | 13.6 | 399 | 80 | 20.1 | 1.31 | (0.98,1.75) | 0.0705 | 1.45 | (0.96,2.18) | |
| Other | 153 | 41 | 26.8 | 165 | 45 | 27.3 | 0.91 | (0.65,1.26) | 0.5615 | 0.86 | (0.49,1.50) | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.3485 |
| Diabetic | 1646 | 380 | 23.1 | 1694 | 435 | 25.7 | 1.09 | (0.97,1.22) | 0.1464 | 1.16 | (0.97,1.39) | |
| Non-Diabetic | 1462 | 320 | 21.9 | 1491 | 344 | 23.1 | 1.00 | (0.89,1.13) | 0.9415 | 1.03 | (0.85,1.25) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2090 |
| <30 | 1868 | 412 | 22.1 | 1843 | 412 | 22.4 | 1.00 | (0.90,1.12) | 0.9699 | 1.02 | (0.85,1.21) | |
| >=30 | 1240 | 288 | 23.2 | 1342 | 367 | 27.3 | 1.12 | (0.98,1.26) | 0.0885 | 1.23 | (1.00,1.51) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.2652 |
| <130 | 1591 | 384 | 24.1 | 1609 | 391 | 24.3 | 1.00 | (0.90,1.12) | 0.9521 | 1.02 | (0.85,1.23) | |
| >=130 | 1517 | 316 | 20.8 | 1576 | 388 | 24.6 | 1.10 | (0.98,1.25) | 0.1161 | 1.20 | (0.99,1.45) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.3: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.8526 |
| <75 | 1574 | 335 | 21.3 | 1541 | 366 | 23.8 | 1.06 | (0.94,1.20) | 0.3116 | 1.11 | (0.92,1.35) | |
| 75 to <85 | 945 | 223 | 23.6 | 1036 | 243 | 23.5 | 1.01 | (0.88,1.17) | 0.8563 | 1.03 | (0.82,1.31) | |
| >=85 | 589 | 142 | 24.1 | 608 | 170 | 28.0 | 1.07 | (0.89,1.29) | 0.4627 | 1.18 | (0.88,1.59) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.2082 |
| <30 | 230 | 50 | 21.7 | 246 | 64 | 26.0 | 1.11 | (0.83,1.49) | 0.4663 | 1.26 | (0.78,2.04) | |
| 30 to <45 | 866 | 165 | 19.1 | 875 | 208 | 23.8 | 1.19 | (1.00,1.41) | 0.0464 | 1.35 | (1.04,1.74) | |
| >=45 | 2011 | 485 | 24.1 | 2064 | 507 | 24.6 | 1.00 | (0.90,1.10) | 0.9849 | 1.00 | (0.85,1.17) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.9947 |
| Normal (<30) | 1168 | 239 | 20.5 | 1203 | 267 | 22.2 | 1.05 | (0.91,1.20) | 0.5390 | 1.07 | (0.86,1.34) | |
| Microalbuminuria (30 to <=300) | 1453 | 337 | 23.2 | 1462 | 375 | 25.6 | 1.04 | (0.92,1.18) | 0.4981 | 1.12 | (0.92,1.35) | |
| Macroalbuminuria (>300) | 478 | 121 | 25.3 | 505 | 131 | 25.9 | 1.06 | (0.87,1.28) | 0.5882 | 1.09 | (0.79,1.52) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.4438 |
| Low, moderate or high | 2305 | 534 | 23.2 | 2394 | 589 | 24.6 | 1.03 | (0.93,1.13) | 0.5763 | 1.05 | (0.91,1.23) | |
| Very high | 794 | 163 | 20.5 | 777 | 184 | 23.7 | 1.11 | (0.93,1.32) | 0.2386 | 1.22 | (0.93,1.60) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.6419 |
| No | 541 | 119 | 22.0 | 547 | 134 | 24.5 | 1.10 | (0.89,1.34) | 0.3790 | 1.18 | (0.86,1.62) | |
| Yes | 2567 | 581 | 22.6 | 2638 | 645 | 24.5 | 1.04 | (0.95,1.14) | 0.4039 | 1.09 | (0.94,1.26) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.3140 |
| No | 317 | 66 | 20.8 | 324 | 68 | 21.0 | 0.91 | (0.69,1.21) | 0.5336 | 0.91 | (0.60,1.40) | |
| Yes | 2791 | 634 | 22.7 | 2861 | 711 | 24.9 | 1.06 | (0.98,1.16) | 0.1639 | 1.12 | (0.98,1.29) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

Table R.5.1.2.1.3: 2 Responder analysis for KCCQ-OSS change from baseline to last value during planned treatment period >= 15 points (improvement) overall and by subgroup - RS (OC-AD)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo: Risk ratio * | (95% CI) | p-value | Odds ratio *** | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | | 0.6034 |
| No | 261 | 49 | 18.8 | 291 | 58 | 19.9 | 1.13 | (0.84,1.53) | 0.4185 | 1.16 | (0.72,1.86) | |
| Yes | 2847 | 651 | 22.9 | 2894 | 721 | 24.9 | 1.04 | (0.96,1.14) | 0.3435 | 1.10 | (0.95,1.26) | |

* Based on a log-linked Poisson model with robust estimate of variance^, ** p-value corresponds to the treatment by subgroup interaction term. *** Based on a logistic regression model^ showing Wald confidence intervals.
^ Models contain terms age, baseline eGFR (CKD-EPI), baseline LVEF, Baseline KCCQ-OSS score, treatment, region, baseline diabetes status, sex, study, subgroup and treatment by subgroup interaction. Covariate removed from model if also used as the subgroup.
N: Number of patients analysed, n: Number of patients with event.

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline)
Subjects without a baseline or post-baseline KCCQ-OSS score are not included in the analysis.
For discontinued subjects, last available value was used. For completing subjects, last value up to last treatment intake + 7 days was used.

**R.5.2**

**R.5.2.1**

R.5.2.1 Adverse events overall

**Figure R.5.2.1: 1**

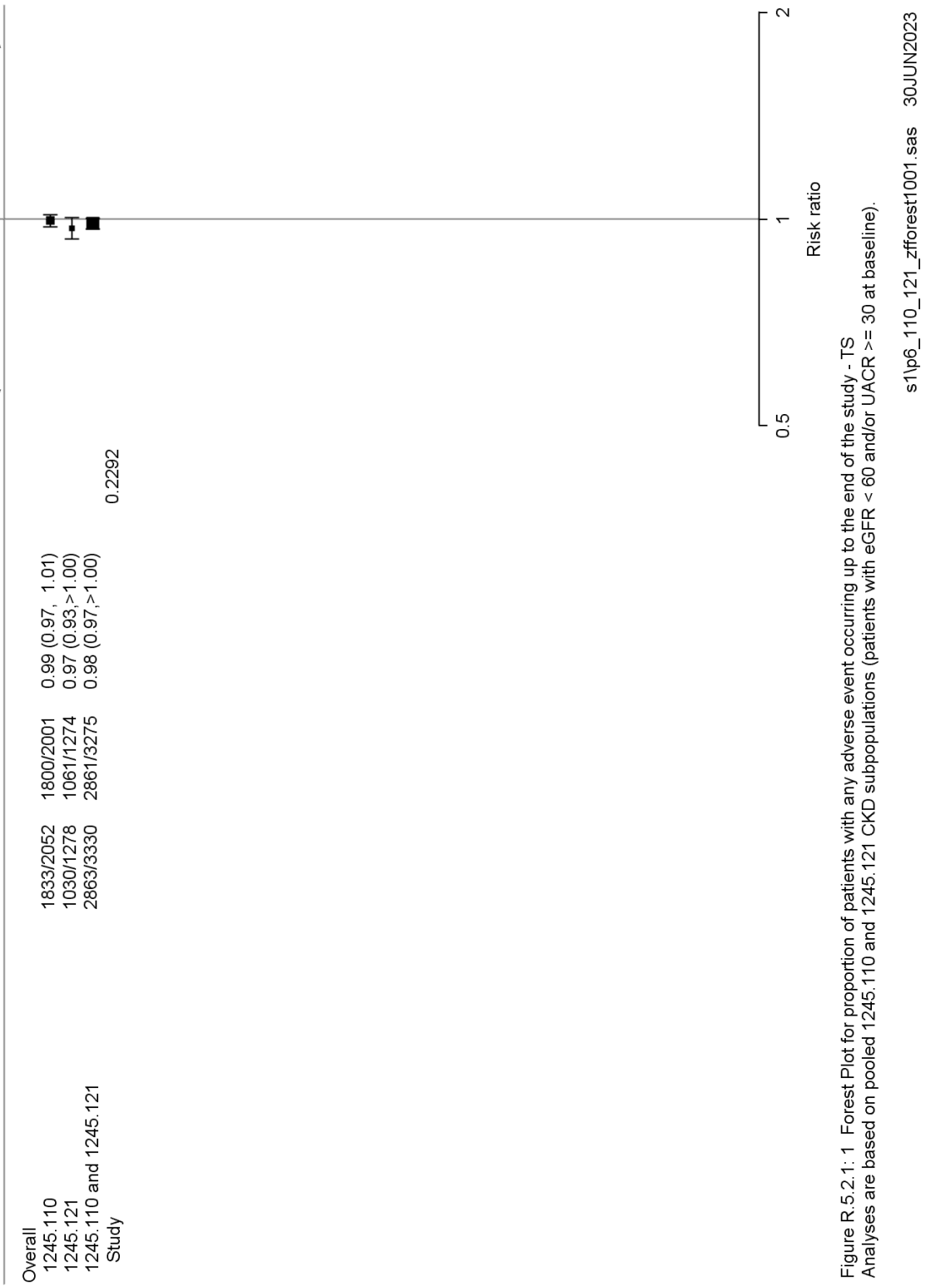


Figure R.5.2.1: 1 Forest Plot for proportion of patients with any adverse event occurring up to the end of the study - TS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.2.1: 1 Proportion of patients with any adverse event occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 2861 | 87.4 | 3330 | 2863 | 86.0 | 0.0871 | 0.98 | (0.97,>1.00) | 0.88 | (0.77,1.02) | -0.01 | (-0.03, 0.00) | |
| Study | | | | | | | | | | | | | | 0.2292 |
| 1245.110 | 2001 | 1800 | 90.0 | 2052 | 1833 | 89.3 | 0.5123 | 0.99 | (0.97, 1.01) | 0.93 | (0.76,1.14) | -0.01 | (-0.03, 0.01) | |
| 1245.121 | 1274 | 1061 | 83.3 | 1278 | 1030 | 80.6 | 0.0778 | 0.97 | (0.93,>1.00) | 0.83 | (0.68,1.02) | -0.03 | (-0.06, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.6440 |
| Male | 2023 | 1753 | 86.7 | 2068 | 1757 | 85.0 | 0.1161 | 0.98 | (0.96,>1.00) | 0.87 | (0.73,1.04) | -0.02 | (-0.04, 0.00) | |
| Female | 1252 | 1108 | 88.5 | 1262 | 1106 | 87.6 | 0.4524 | 0.99 | (0.96, 1.02) | 0.91 | (0.71,1.16) | -0.01 | (-0.03, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.3751 |
| <65 | 766 | 641 | 83.7 | 705 | 591 | 83.8 | 0.9841 | 1.00 | (0.96, 1.05) | 1.00 | (0.76,1.33) | 0.00 | (-0.04, 0.04) | |
| >=65 | 2509 | 2220 | 88.5 | 2625 | 2272 | 86.6 | 0.0380 | 0.98 | (0.96,<1.00) | 0.84 | (0.71,0.99) | -0.02 | (-0.04, 0.00) | |
| Region | | | | | | | | | | | | | | 0.9000 |
| North America | 434 | 408 | 94.0 | 432 | 400 | 92.6 | 0.3923 | 0.98 | (0.95, 1.02) | 0.79 | (0.46,1.36) | -0.01 | (-0.05, 0.02) | |
| Latin America | 931 | 794 | 85.3 | 944 | 785 | 83.2 | 0.2386 | 0.98 | (0.94, 1.02) | 0.86 | (0.67,1.11) | -0.02 | (-0.05, 0.01) | |
| Europe | 1334 | 1132 | 84.9 | 1361 | 1137 | 83.5 | 0.3287 | 0.98 | (0.95, 1.02) | 0.90 | (0.73,1.11) | -0.01 | (-0.04, 0.01) | |
| Asia | 405 | 379 | 93.6 | 413 | 381 | 92.3 | 0.4288 | 0.98 | (0.95, 1.02) | 0.80 | (0.47,1.38) | -0.01 | (-0.05, 0.02) | |
| Other | 171 | 148 | 86.5 | 180 | 160 | 88.9 | 0.5760 | 1.02 | (0.95, 1.10) | 1.20 | (0.63,2.30) | 0.02 | (-0.05, 0.09) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4474 |
| Diabetic | 1739 | 1523 | 87.6 | 1779 | 1544 | 86.8 | 0.4517 | 0.99 | (0.97, 1.02) | 0.93 | (0.76,1.13) | -0.01 | (-0.03, 0.01) | |
| Non-Diabetic | 1536 | 1338 | 87.1 | 1551 | 1319 | 85.0 | 0.0913 | 0.98 | (0.95,>1.00) | 0.84 | (0.68,1.03) | -0.02 | (-0.05, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5730 |
| <30 | 1975 | 1725 | 87.3 | 1930 | 1669 | 86.5 | 0.3493 | 0.99 | (0.96, 1.01) | 0.91 | (0.76,1.10) | -0.01 | (-0.03, 0.01) | |
| >=30 | 1300 | 1136 | 87.4 | 1400 | 1194 | 85.3 | 0.1389 | 0.98 | (0.95, 1.01) | 0.85 | (0.68,1.06) | -0.02 | (-0.05, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7597 |
| <130 | 1684 | 1463 | 86.9 | 1687 | 1448 | 85.8 | 0.3211 | 0.99 | (0.96, 1.01) | 0.90 | (0.74,1.10) | -0.01 | (-0.03, 0.01) | |
| >=130 | 1591 | 1398 | 87.9 | 1643 | 1415 | 86.1 | 0.1527 | 0.98 | (0.96, 1.01) | 0.86 | (0.70,1.06) | -0.02 | (-0.04, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.1: 1 Proportion of patients with any adverse event occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0151 |
| <75 | 1653 | 1445 | 87.4 | 1612 | 1428 | 88.6 | 0.3429 | 1.01 | (0.99, 1.04) | 1.11 | (0.90,1.37) | 0.01 | (-0.01, 0.03) | |
| 75 to <85 | 1005 | 869 | 86.5 | 1085 | 898 | 82.8 | 0.0202 | 0.96 | (0.92, 0.99) | 0.75 | (0.59,0.96) | -0.04 | (-0.07,-0.01) | |
| >=85 | 617 | 547 | 88.7 | 633 | 537 | 84.8 | 0.0489 | 0.96 | (0.92,<1.00) | 0.72 | (0.51,1.00) | -0.04 | (-0.07, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1229 |
| <30 | 250 | 230 | 92.0 | 263 | 249 | 94.7 | 0.1949 | 1.03 | (0.98, 1.08) | 1.59 | (0.78,3.23) | 0.03 | (-0.01, 0.07) | |
| 30 to <45 | 898 | 803 | 89.4 | 909 | 792 | 87.1 | 0.1200 | 0.97 | (0.94, 1.01) | 0.80 | (0.60,1.06) | -0.02 | (-0.05, 0.01) | |
| >=45 | 2126 | 1827 | 85.9 | 2158 | 1822 | 84.4 | 0.1289 | 0.98 | (0.96, 1.01) | 0.88 | (0.74,1.04) | -0.02 | (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7686 |
| Normal (<30) | 1216 | 1036 | 85.2 | 1243 | 1052 | 84.6 | 0.6727 | 0.99 | (0.96, 1.03) | 0.95 | (0.76,1.19) | -0.01 | (-0.03, 0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 1358 | 87.7 | 1546 | 1327 | 85.8 | 0.1041 | 0.98 | (0.95,>1.00) | 0.84 | (0.68,1.04) | -0.02 | (-0.04, 0.00) | |
| Macroalbuminuria (>300) | 500 | 459 | 91.8 | 525 | 475 | 90.5 | 0.4970 | 0.99 | (0.95, 1.02) | 0.86 | (0.56,1.33) | -0.01 | (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2120 |
| Low, moderate or high | 2430 | 2085 | 85.8 | 2495 | 2099 | 84.1 | 0.0789 | 0.98 | (0.96,>1.00) | 0.87 | (0.74,1.02) | -0.02 | (-0.04, 0.00) | |
| Very high | 834 | 768 | 92.1 | 820 | 756 | 92.2 | 0.8751 | 1.00 | (0.97, 1.03) | 1.03 | (0.72,1.48) | 0.00 | (-0.02, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5651 |
| No | 572 | 518 | 90.6 | 578 | 509 | 88.1 | 0.1798 | 0.97 | (0.94, 1.01) | 0.77 | (0.53,1.13) | -0.02 | (-0.06, 0.01) | |
| Yes | 2703 | 2343 | 86.7 | 2752 | 2354 | 85.5 | 0.1945 | 0.99 | (0.97, 1.01) | 0.90 | (0.77,1.05) | -0.01 | (-0.03, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8908 |
| No | 344 | 312 | 90.7 | 349 | 312 | 89.4 | 0.6015 | 0.99 | (0.94, 1.04) | 0.88 | (0.53,1.44) | -0.01 | (-0.06, 0.03) | |
| Yes | 2931 | 2549 | 87.0 | 2981 | 2551 | 85.6 | 0.1007 | 0.98 | (0.96,>1.00) | 0.88 | (0.76,1.02) | -0.01 | (-0.03, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5845 |
| No | 275 | 244 | 88.7 | 307 | 263 | 85.7 | 0.3023 | 0.97 | (0.91, 1.03) | 0.77 | (0.47,1.26) | -0.03 | (-0.08, 0.03) | |
| Yes | 3000 | 2617 | 87.2 | 3023 | 2600 | 86.0 | 0.1463 | 0.99 | (0.97, 1.01) | 0.90 | (0.77,1.04) | -0.01 | (-0.03, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

**Figure R.5.2.1: 2**

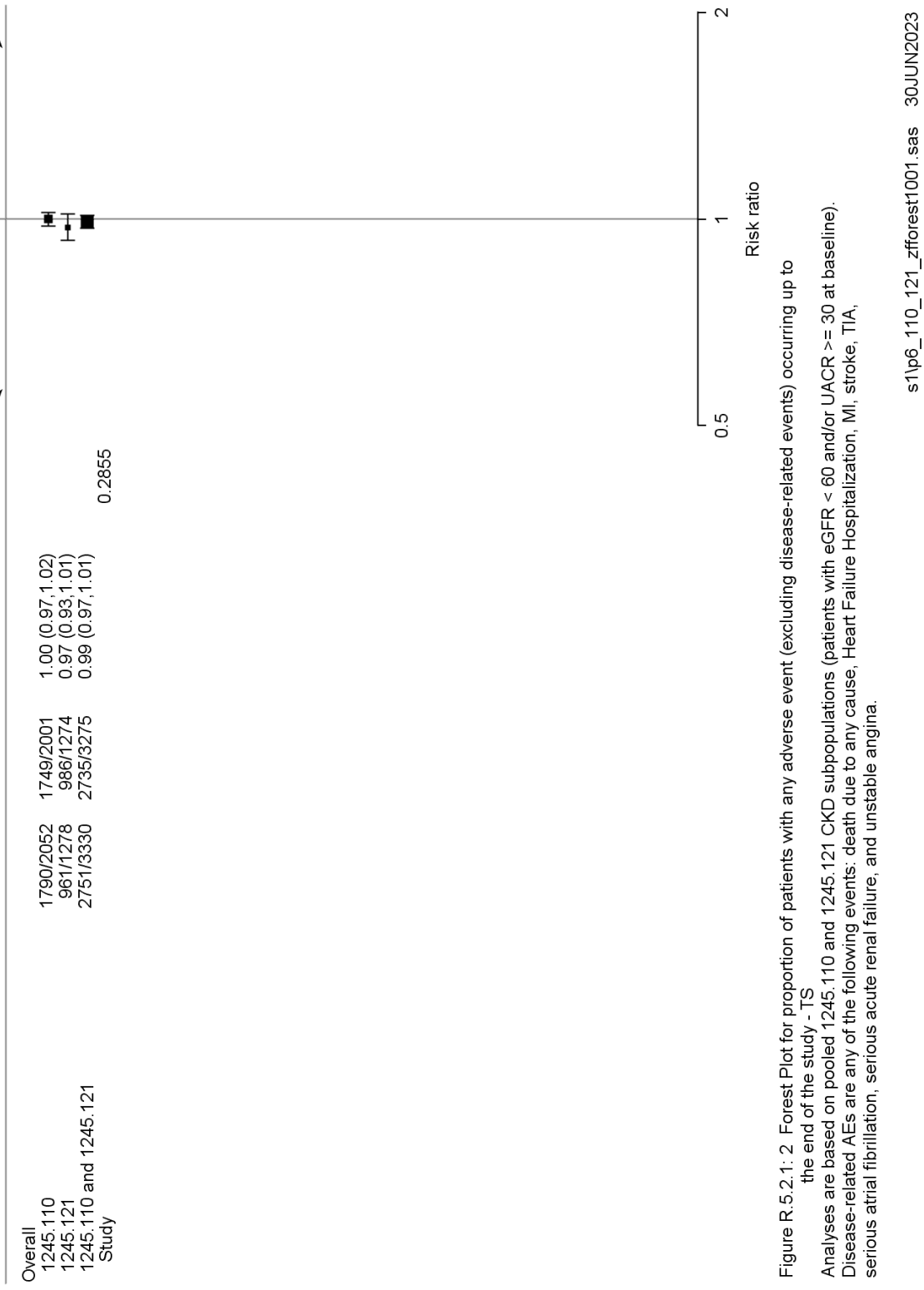


Figure R.5.2.1: 2 Forest Plot for proportion of patients with any adverse event (excluding disease-related events) occurring up to the end of the study - TS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.

Table R.5.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 2735 | 83.5 | 3330 | 2751 | 82.6 | 0.2953 | 0.99 | (0.97, 1.01) | 0.93 | (0.82,1.06) | -0.01 | (-0.03,0.01) | |
| Study | | | | | | | | | | | | | | 0.2855 |
| 1245.110 | 2001 | 1749 | 87.4 | 2052 | 1790 | 87.2 | 0.8676 | 1.00 | (0.97, 1.02) | 0.98 | (0.82,1.18) | 0.00 | (-0.02,0.02) | |
| 1245.121 | 1274 | 986 | 77.4 | 1278 | 961 | 75.2 | 0.1917 | 0.97 | (0.93, 1.01) | 0.89 | (0.74,1.06) | -0.02 | (-0.05,0.01) | |
| Sex | | | | | | | | | | | | | | 0.9452 |
| Male | 2023 | 1663 | 82.2 | 2068 | 1680 | 81.2 | 0.4095 | 0.99 | (0.96, 1.02) | 0.93 | (0.80,1.10) | -0.01 | (-0.03,0.01) | |
| Female | 1252 | 1072 | 85.6 | 1262 | 1071 | 84.9 | 0.5197 | 0.99 | (0.96, 1.02) | 0.93 | (0.74,1.16) | -0.01 | (-0.04,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.4809 |
| <65 | 766 | 605 | 79.0 | 705 | 560 | 79.4 | 0.8836 | 1.00 | (0.95, 1.06) | 1.02 | (0.79,1.32) | 0.00 | (-0.04,0.04) | |
| >=65 | 2509 | 2130 | 84.9 | 2625 | 2191 | 83.5 | 0.1672 | 0.98 | (0.96, 1.01) | 0.90 | (0.77,1.05) | -0.01 | (-0.03,0.01) | |
| Region | | | | | | | | | | | | | | 0.7593 |
| North America | 434 | 395 | 91.0 | 432 | 391 | 90.5 | 0.7833 | 0.99 | (0.95, 1.04) | 0.94 | (0.59,1.49) | -0.01 | (-0.04,0.03) | |
| Latin America | 931 | 746 | 80.1 | 944 | 733 | 77.6 | 0.2244 | 0.97 | (0.93, 1.02) | 0.87 | (0.69,1.09) | -0.02 | (-0.06,0.01) | |
| Europe | 1334 | 1077 | 80.7 | 1361 | 1092 | 80.2 | 0.7022 | 0.99 | (0.96, 1.03) | 0.96 | (0.80,1.17) | -0.01 | (-0.04,0.02) | |
| Asia | 405 | 372 | 91.9 | 413 | 376 | 91.0 | 0.6332 | 0.99 | (0.95, 1.03) | 0.89 | (0.54,1.45) | -0.01 | (-0.05,0.03) | |
| Other | 171 | 145 | 84.8 | 180 | 159 | 88.3 | 0.3932 | 1.04 | (0.96, 1.12) | 1.32 | (0.70,2.47) | 0.03 | (-0.04,0.10) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.1236 |
| Diabetic | 1739 | 1447 | 83.2 | 1779 | 1488 | 83.6 | 0.7744 | 1.00 | (0.98, 1.03) | 1.03 | (0.86,1.23) | 0.00 | (-0.02,0.03) | |
| Non-Diabetic | 1536 | 1288 | 83.9 | 1551 | 1263 | 81.4 | 0.0688 | 0.97 | (0.94,>1.00) | 0.84 | (0.70,1.01) | -0.02 | (-0.05,0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7072 |
| <30 | 1975 | 1648 | 83.4 | 1930 | 1602 | 83.0 | 0.5935 | 0.99 | (0.97, 1.02) | 0.95 | (0.81,1.13) | -0.01 | (-0.03,0.02) | |
| >=30 | 1300 | 1087 | 83.6 | 1400 | 1149 | 82.1 | 0.3569 | 0.98 | (0.95, 1.02) | 0.91 | (0.74,1.11) | -0.01 | (-0.04,0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5796 |
| <130 | 1684 | 1393 | 82.7 | 1687 | 1374 | 81.4 | 0.2694 | 0.98 | (0.95, 1.01) | 0.90 | (0.76,1.08) | -0.01 | (-0.04,0.01) | |
| >=130 | 1591 | 1342 | 84.3 | 1643 | 1377 | 83.8 | 0.7226 | 0.99 | (0.97, 1.02) | 0.97 | (0.80,1.17) | 0.00 | (-0.03,0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0321 |
| <75 | 1653 | 1379 | 83.4 | 1612 | 1372 | 85.1 | 0.2216 | 1.02 | (0.99, 1.05) | 1.13 | (0.93,1.36) | 0.02 | (-0.01,0.04) | |
| 75 to <85 | 1005 | 828 | 82.4 | 1085 | 856 | 78.9 | 0.0458 | 0.96 | (0.92,<1.00) | 0.80 | (0.64,1.00) | -0.03 | (-0.07,0.00) | |
| >=85 | 617 | 528 | 85.6 | 633 | 523 | 82.6 | 0.1610 | 0.97 | (0.92, 1.01) | 0.80 | (0.59,1.09) | -0.03 | (-0.07,0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1577 |
| <30 | 250 | 220 | 88.0 | 263 | 241 | 91.6 | 0.1399 | 1.04 | (0.99, 1.11) | 1.55 | (0.86,2.78) | 0.04 | (-0.01,0.09) | |
| 30 to <45 | 898 | 770 | 85.7 | 909 | 765 | 84.2 | 0.3136 | 0.98 | (0.94, 1.02) | 0.88 | (0.68,1.14) | -0.02 | (-0.05,0.02) | |
| >=45 | 2126 | 1744 | 82.0 | 2158 | 1745 | 80.9 | 0.2525 | 0.98 | (0.96, 1.01) | 0.91 | (0.78,1.07) | -0.01 | (-0.04,0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9918 |
| Normal (<30) | 1216 | 1004 | 82.6 | 1243 | 1014 | 81.6 | 0.4945 | 0.99 | (0.95, 1.02) | 0.93 | (0.75,1.15) | -0.01 | (-0.04,0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 1285 | 83.0 | 1546 | 1271 | 82.2 | 0.4963 | 0.99 | (0.96, 1.02) | 0.94 | (0.78,1.13) | -0.01 | (-0.04,0.02) | |
| Macroalbuminuria (>300) | 500 | 440 | 88.0 | 525 | 457 | 87.0 | 0.7021 | 0.99 | (0.95, 1.04) | 0.93 | (0.64,1.35) | -0.01 | (-0.05,0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5289 |
| Low, moderate or high | 2430 | 1988 | 81.8 | 2495 | 2016 | 80.8 | 0.2932 | 0.99 | (0.96, 1.01) | 0.93 | (0.80,1.07) | -0.01 | (-0.03,0.01) | |
| Very high | 834 | 741 | 88.8 | 820 | 727 | 88.7 | 0.9827 | 1.00 | (0.97, 1.03) | 1.00 | (0.73,1.36) | 0.00 | (-0.03,0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6496 |
| No | 572 | 496 | 86.7 | 578 | 490 | 84.8 | 0.3674 | 0.98 | (0.93, 1.03) | 0.86 | (0.61,1.20) | -0.02 | (-0.06,0.02) | |
| Yes | 2703 | 2239 | 82.8 | 2752 | 2261 | 82.2 | 0.4509 | 0.99 | (0.97, 1.02) | 0.95 | (0.82,1.09) | -0.01 | (-0.03,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7366 |
| No | 344 | 298 | 86.6 | 349 | 301 | 86.2 | 0.9481 | 1.00 | (0.94, 1.06) | 0.99 | (0.64,1.53) | 0.00 | (-0.05,0.05) | |
| Yes | 2931 | 2437 | 83.1 | 2981 | 2450 | 82.2 | 0.2777 | 0.99 | (0.96, 1.01) | 0.93 | (0.81,1.06) | -0.01 | (-0.03,0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.1: 2 Proportion of patients with any adverse event (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8600 |
| No | 275 | 235 | 85.5 | 307 | 257 | 83.7 | 0.6231 | 0.98 | (0.92, 1.05) | 0.89 | (0.56,1.41) | -0.01 | (-0.07,0.04) | |
| Yes | 3000 | 2500 | 83.3 | 3023 | 2494 | 82.5 | 0.3533 | 0.99 | (0.97, 1.01) | 0.94 | (0.82,1.07) | -0.01 | (-0.03,0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

**Figure R.5.2.1: 3**

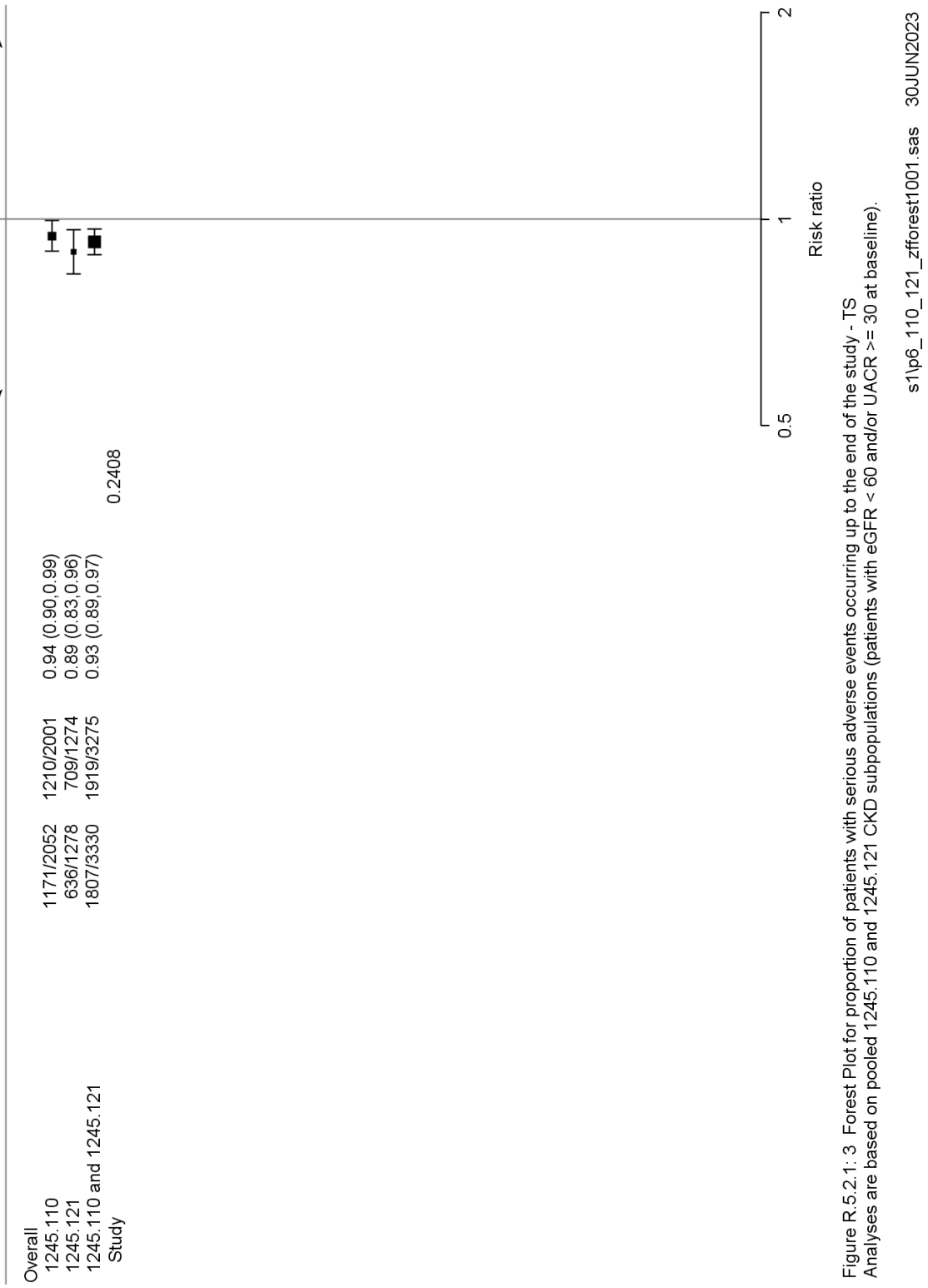


Figure R.5.2.1: 3 Forest Plot for proportion of patients with serious adverse events occurring up to the end of the study - TS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.2.1: 3 Proportion of patients with serious adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 1919 | 58.6 | 3330 | 1807 | 54.3 | 0.0003 | 0.93 | (0.89, 0.97) | 0.84 | (0.76,0.92) | -0.04 | (-0.07,-0.02) | |
| Study | | | | | | | | | | | | | | 0.2408 |
| 1245.110 | 2001 | 1210 | 60.5 | 2052 | 1171 | 57.1 | 0.0278 | 0.94 | (0.90, 0.99) | 0.87 | (0.77,0.98) | -0.03 | (-0.06, 0.00) | |
| 1245.121 | 1274 | 709 | 55.7 | 1278 | 636 | 49.8 | 0.0029 | 0.89 | (0.83, 0.96) | 0.79 | (0.68,0.92) | -0.06 | (-0.10,-0.02) | |
| Sex | | | | | | | | | | | | | | 0.9811 |
| Male | 2023 | 1215 | 60.1 | 2068 | 1149 | 55.6 | 0.0034 | 0.92 | (0.88, 0.97) | 0.83 | (0.73,0.94) | -0.05 | (-0.08,-0.01) | |
| Female | 1252 | 704 | 56.2 | 1262 | 658 | 52.1 | 0.0356 | 0.93 | (0.86, 0.99) | 0.84 | (0.72,0.99) | -0.04 | (-0.08, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.6840 |
| <65 | 766 | 422 | 55.1 | 705 | 353 | 50.1 | 0.0517 | 0.91 | (0.82,>1.00) | 0.82 | (0.66,1.00) | -0.05 | (-0.10, 0.00) | |
| >=65 | 2509 | 1497 | 59.7 | 2625 | 1454 | 55.4 | 0.0020 | 0.93 | (0.89, 0.97) | 0.84 | (0.75,0.94) | -0.04 | (-0.07,-0.02) | |
| Region | | | | | | | | | | | | | | 0.8070 |
| North America | 434 | 295 | 68.0 | 432 | 284 | 65.7 | 0.4805 | 0.97 | (0.88, 1.06) | 0.90 | (0.68,1.20) | -0.02 | (-0.09, 0.04) | |
| Latin America | 931 | 525 | 56.4 | 944 | 490 | 51.9 | 0.0578 | 0.92 | (0.85,>1.00) | 0.84 | (0.70,1.01) | -0.04 | (-0.09, 0.00) | |
| Europe | 1334 | 748 | 56.1 | 1361 | 710 | 52.2 | 0.0406 | 0.93 | (0.87,<1.00) | 0.85 | (0.73,0.99) | -0.04 | (-0.08, 0.00) | |
| Asia | 405 | 253 | 62.5 | 413 | 233 | 56.4 | 0.0779 | 0.90 | (0.81, 1.01) | 0.78 | (0.59,1.03) | -0.06 | (-0.13, 0.01) | |
| Other | 171 | 98 | 57.3 | 180 | 90 | 50.0 | 0.1185 | 0.86 | (0.71, 1.04) | 0.71 | (0.46,1.09) | -0.08 | (-0.18, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7590 |
| Diabetic | 1739 | 1045 | 60.1 | 1779 | 996 | 56.0 | 0.0125 | 0.93 | (0.88, 0.98) | 0.84 | (0.74,0.96) | -0.04 | (-0.07,-0.01) | |
| Non-Diabetic | 1536 | 874 | 56.9 | 1551 | 811 | 52.3 | 0.0097 | 0.92 | (0.86, 0.98) | 0.83 | (0.72,0.96) | -0.05 | (-0.08,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0154 |
| <30 | 1975 | 1178 | 59.6 | 1930 | 1022 | 53.0 | <0.0001 | 0.89 | (0.84, 0.94) | 0.76 | (0.67,0.86) | -0.07 | (-0.10,-0.04) | |
| >=30 | 1300 | 741 | 57.0 | 1400 | 785 | 56.1 | 0.6730 | 0.99 | (0.92, 1.05) | 0.97 | (0.83,1.13) | -0.01 | (-0.05, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5556 |
| <130 | 1684 | 993 | 59.0 | 1687 | 911 | 54.0 | 0.0030 | 0.91 | (0.86, 0.97) | 0.81 | (0.71,0.93) | -0.05 | (-0.08,-0.02) | |
| >=130 | 1591 | 926 | 58.2 | 1643 | 896 | 54.5 | 0.0380 | 0.94 | (0.88,<1.00) | 0.86 | (0.75,0.99) | -0.04 | (-0.07, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.1: 3 Proportion of patients with serious adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2232 |
| <75 | 1653 | 986 | 59.6 | 1612 | 926 | 57.4 | 0.1834 | 0.96 | (0.91, 1.02) | 0.91 | (0.79,1.05) | -0.02 | (-0.06, 0.01) | |
| 75 to <85 | 1005 | 569 | 56.6 | 1085 | 550 | 50.7 | 0.0069 | 0.90 | (0.83, 0.97) | 0.79 | (0.66,0.94) | -0.06 | (-0.10,-0.02) | |
| >=85 | 617 | 364 | 59.0 | 633 | 331 | 52.3 | 0.0177 | 0.89 | (0.80, 0.98) | 0.76 | (0.61,0.95) | -0.07 | (-0.12,-0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2270 |
| <30 | 250 | 176 | 70.4 | 263 | 187 | 71.1 | 0.7537 | 1.02 | (0.91, 1.14) | 1.06 | (0.73,1.56) | 0.01 | (-0.07, 0.09) | |
| 30 to <45 | 898 | 557 | 62.0 | 909 | 520 | 57.2 | 0.0334 | 0.92 | (0.85, 0.99) | 0.81 | (0.67,0.98) | -0.05 | (-0.09, 0.00) | |
| >=45 | 2126 | 1186 | 55.8 | 2158 | 1100 | 51.0 | 0.0013 | 0.91 | (0.86, 0.97) | 0.82 | (0.73,0.93) | -0.05 | (-0.08,-0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9904 |
| Normal (<30) | 1216 | 650 | 53.5 | 1243 | 618 | 49.7 | 0.0608 | 0.93 | (0.86,>1.00) | 0.86 | (0.73,1.01) | -0.04 | (-0.08, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 927 | 59.9 | 1546 | 857 | 55.4 | 0.0108 | 0.92 | (0.87, 0.98) | 0.83 | (0.72,0.96) | -0.05 | (-0.08,-0.01) | |
| Macroalbuminuria (>300) | 500 | 336 | 67.2 | 525 | 328 | 62.5 | 0.1189 | 0.93 | (0.85, 1.02) | 0.81 | (0.63,1.05) | -0.05 | (-0.10, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1480 |
| Low, moderate or high | 2430 | 1351 | 55.6 | 2495 | 1267 | 50.8 | 0.0006 | 0.91 | (0.87, 0.96) | 0.82 | (0.73,0.92) | -0.05 | (-0.08,-0.02) | |
| Very high | 834 | 563 | 67.5 | 820 | 537 | 65.5 | 0.4152 | 0.97 | (0.91, 1.04) | 0.92 | (0.75,1.13) | -0.02 | (-0.06, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5718 |
| No | 572 | 371 | 64.9 | 578 | 355 | 61.4 | 0.2321 | 0.95 | (0.87, 1.04) | 0.86 | (0.68,1.10) | -0.03 | (-0.09, 0.02) | |
| Yes | 2703 | 1548 | 57.3 | 2752 | 1452 | 52.8 | 0.0007 | 0.92 | (0.88, 0.97) | 0.83 | (0.75,0.93) | -0.05 | (-0.07,-0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8801 |
| No | 344 | 213 | 61.9 | 349 | 198 | 56.7 | 0.1700 | 0.92 | (0.81, 1.04) | 0.81 | (0.60,1.10) | -0.05 | (-0.12, 0.02) | |
| Yes | 2931 | 1706 | 58.2 | 2981 | 1609 | 54.0 | 0.0009 | 0.93 | (0.89, 0.97) | 0.84 | (0.76,0.93) | -0.04 | (-0.07,-0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2073 |
| No | 275 | 153 | 55.6 | 307 | 143 | 46.6 | 0.0323 | 0.84 | (0.72, 0.99) | 0.70 | (0.50,0.97) | -0.09 | (-0.17,-0.01) | |
| Yes | 3000 | 1766 | 58.9 | 3023 | 1664 | 55.0 | 0.0025 | 0.93 | (0.89, 0.98) | 0.85 | (0.77,0.95) | -0.04 | (-0.06,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

**Figure R.5.2.1: 4**

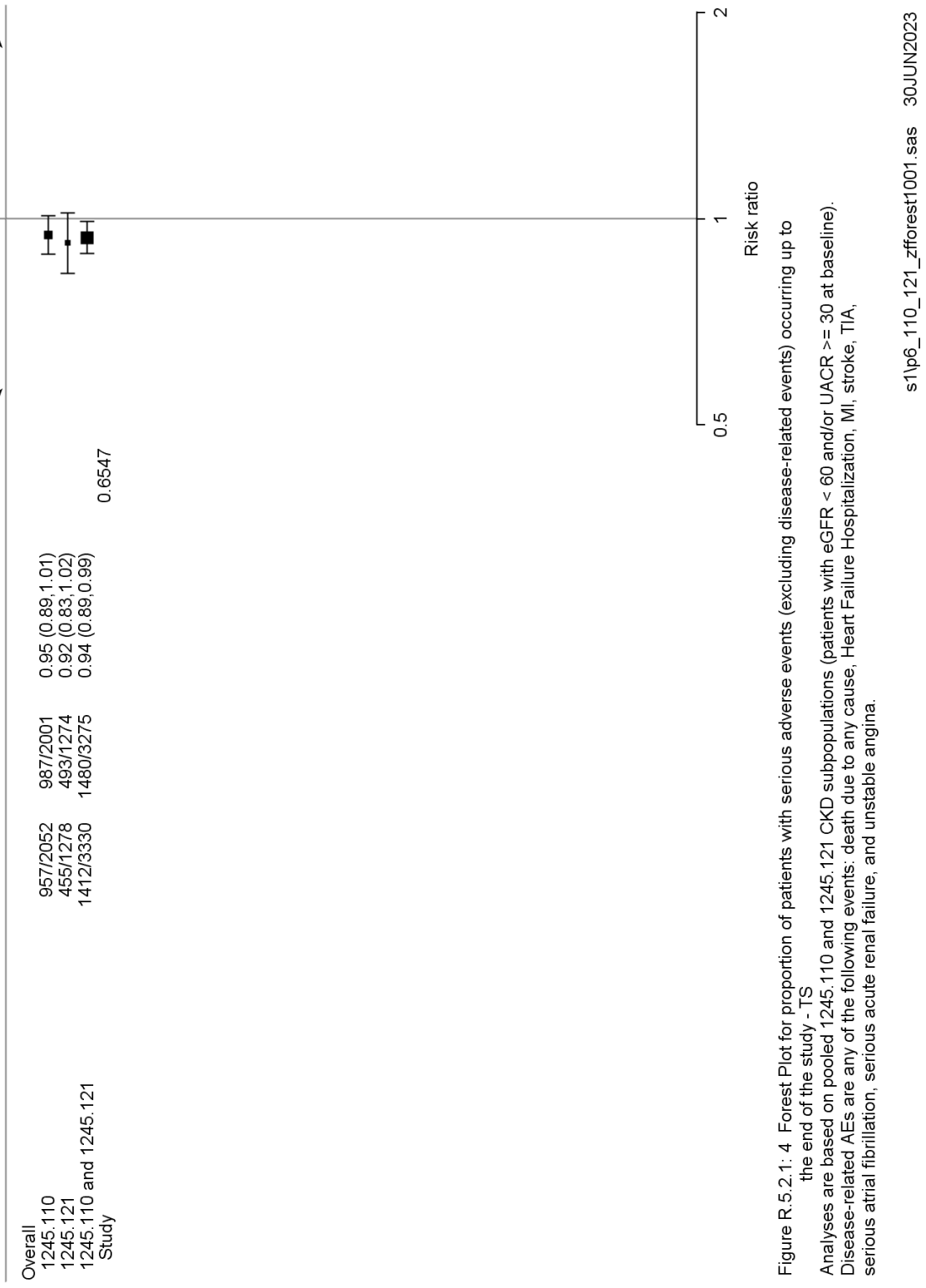


Figure R.5.2.1: 4 Forest Plot for proportion of patients with serious adverse events (excluding disease-related events) occurring up to the end of the study - TS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.

Table R.5.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 1480 | 45.2 | 3330 | 1412 | 42.4 | 0.0191 | 0.94 | (0.89, 0.99) | 0.89 | (0.81,0.98) | -0.03 | (-0.05, 0.00) | |
| Study | | | | | | | | | | | | | | 0.6547 |
| 1245.110 | 2001 | 987 | 49.3 | 2052 | 957 | 46.6 | 0.0868 | 0.95 | (0.89, 1.01) | 0.90 | (0.79,1.02) | -0.03 | (-0.06, 0.00) | |
| 1245.121 | 1274 | 493 | 38.7 | 1278 | 455 | 35.6 | 0.1058 | 0.92 | (0.83, 1.02) | 0.88 | (0.75,1.03) | -0.03 | (-0.07, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.9962 |
| Male | 2023 | 930 | 46.0 | 2068 | 891 | 43.1 | 0.0590 | 0.94 | (0.88,>1.00) | 0.89 | (0.78,1.00) | -0.03 | (-0.06, 0.00) | |
| Female | 1252 | 550 | 43.9 | 1262 | 521 | 41.3 | 0.1579 | 0.94 | (0.86, 1.03) | 0.89 | (0.76,1.05) | -0.03 | (-0.07, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.9581 |
| <65 | 766 | 300 | 39.2 | 705 | 258 | 36.6 | 0.2896 | 0.93 | (0.82, 1.06) | 0.89 | (0.72,1.10) | -0.03 | (-0.08, 0.02) | |
| >=65 | 2509 | 1180 | 47.0 | 2625 | 1154 | 44.0 | 0.0282 | 0.94 | (0.88, 0.99) | 0.88 | (0.79,0.99) | -0.03 | (-0.06, 0.00) | |
| Region | | | | | | | | | | | | | | 0.8731 |
| North America | 434 | 252 | 58.1 | 432 | 247 | 57.2 | 0.7820 | 0.98 | (0.88, 1.10) | 0.96 | (0.73,1.26) | -0.01 | (-0.07, 0.06) | |
| Latin America | 931 | 381 | 40.9 | 944 | 350 | 37.1 | 0.1023 | 0.91 | (0.81, 1.02) | 0.86 | (0.71,1.03) | -0.04 | (-0.08, 0.01) | |
| Europe | 1334 | 583 | 43.7 | 1361 | 559 | 41.1 | 0.1549 | 0.94 | (0.86, 1.02) | 0.89 | (0.77,1.04) | -0.03 | (-0.06, 0.01) | |
| Asia | 405 | 187 | 46.2 | 413 | 183 | 44.3 | 0.5645 | 0.96 | (0.82, 1.11) | 0.92 | (0.70,1.21) | -0.02 | (-0.09, 0.05) | |
| Other | 171 | 77 | 45.0 | 180 | 73 | 40.6 | 0.3142 | 0.89 | (0.70, 1.12) | 0.80 | (0.52,1.23) | -0.05 | (-0.15, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.1794 |
| Diabetic | 1739 | 786 | 45.2 | 1779 | 781 | 43.9 | 0.4091 | 0.97 | (0.90, 1.04) | 0.95 | (0.83,1.08) | -0.01 | (-0.05, 0.02) | |
| Non-Diabetic | 1536 | 694 | 45.2 | 1551 | 631 | 40.7 | 0.0105 | 0.90 | (0.83, 0.98) | 0.83 | (0.72,0.96) | -0.05 | (-0.08,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1232 |
| <30 | 1975 | 895 | 45.3 | 1930 | 794 | 41.1 | 0.0058 | 0.90 | (0.84, 0.97) | 0.84 | (0.74,0.95) | -0.04 | (-0.07,-0.01) | |
| >=30 | 1300 | 585 | 45.0 | 1400 | 618 | 44.1 | 0.7405 | 0.99 | (0.91, 1.07) | 0.97 | (0.84,1.14) | -0.01 | (-0.04, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3912 |
| <130 | 1684 | 752 | 44.7 | 1687 | 692 | 41.0 | 0.0242 | 0.91 | (0.85, 0.99) | 0.85 | (0.74,0.98) | -0.04 | (-0.07,-0.01) | |
| >=130 | 1591 | 728 | 45.8 | 1643 | 720 | 43.8 | 0.2861 | 0.96 | (0.89, 1.04) | 0.93 | (0.81,1.07) | -0.02 | (-0.05, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2993 |
| <75 | 1653 | 758 | 45.9 | 1612 | 725 | 45.0 | 0.5484 | 0.98 | (0.91, 1.05) | 0.96 | (0.83,1.10) | -0.01 | (-0.04, 0.02) | |
| 75 to <85 | 1005 | 439 | 43.7 | 1085 | 432 | 39.8 | 0.0768 | 0.91 | (0.83, 1.01) | 0.85 | (0.72,1.02) | -0.04 | (-0.08, 0.00) | |
| >=85 | 617 | 283 | 45.9 | 633 | 255 | 40.3 | 0.0480 | 0.88 | (0.77,<1.00) | 0.80 | (0.64,1.00) | -0.06 | (-0.11, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0540 |
| <30 | 250 | 133 | 53.2 | 263 | 153 | 58.2 | 0.1663 | 1.12 | (0.96, 1.30) | 1.28 | (0.90,1.83) | 0.06 | (-0.02, 0.15) | |
| 30 to <45 | 898 | 446 | 49.7 | 909 | 404 | 44.4 | 0.0206 | 0.89 | (0.81, 0.98) | 0.80 | (0.66,0.97) | -0.05 | (-0.10,-0.01) | |
| >=45 | 2126 | 901 | 42.4 | 2158 | 855 | 39.6 | 0.0549 | 0.93 | (0.87,>1.00) | 0.89 | (0.79,1.00) | -0.03 | (-0.06, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7831 |
| Normal (<30) | 1216 | 530 | 43.6 | 1243 | 501 | 40.3 | 0.0918 | 0.92 | (0.84, 1.01) | 0.87 | (0.74,1.02) | -0.03 | (-0.07, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 690 | 44.6 | 1546 | 662 | 42.8 | 0.2878 | 0.96 | (0.88, 1.04) | 0.93 | (0.80,1.07) | -0.02 | (-0.05, 0.02) | |
| Macroalbuminuria (>300) | 500 | 256 | 51.2 | 525 | 246 | 46.9 | 0.1779 | 0.92 | (0.81, 1.04) | 0.84 | (0.66,1.08) | -0.04 | (-0.10, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2743 |
| Low, moderate or high | 2430 | 1045 | 43.0 | 2495 | 994 | 39.8 | 0.0187 | 0.92 | (0.86, 0.99) | 0.87 | (0.78,0.98) | -0.03 | (-0.06,-0.01) | |
| Very high | 834 | 432 | 51.8 | 820 | 416 | 50.7 | 0.7425 | 0.98 | (0.90, 1.08) | 0.97 | (0.80,1.18) | -0.01 | (-0.06, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4680 |
| No | 572 | 289 | 50.5 | 578 | 284 | 49.1 | 0.6601 | 0.97 | (0.87, 1.09) | 0.95 | (0.75,1.20) | -0.01 | (-0.07, 0.04) | |
| Yes | 2703 | 1191 | 44.1 | 2752 | 1128 | 41.0 | 0.0176 | 0.93 | (0.87, 0.99) | 0.88 | (0.79,0.98) | -0.03 | (-0.06,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7388 |
| No | 344 | 170 | 49.4 | 349 | 165 | 47.3 | 0.6067 | 0.96 | (0.82, 1.12) | 0.92 | (0.69,1.25) | -0.02 | (-0.09, 0.05) | |
| Yes | 2931 | 1310 | 44.7 | 2981 | 1247 | 41.8 | 0.0209 | 0.93 | (0.88, 0.99) | 0.89 | (0.80,0.98) | -0.03 | (-0.05, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.1: 4 Proportion of patients with serious adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3309 |
| No | 275 | 124 | 45.1 | 307 | 118 | 38.4 | 0.1136 | 0.86 | (0.71, 1.04) | 0.77 | (0.55,1.07) | -0.06 | (-0.14, 0.02) | |
| Yes | 3000 | 1356 | 45.2 | 3023 | 1294 | 42.8 | 0.0534 | 0.95 | (0.89,>1.00) | 0.90 | (0.82,1.00) | -0.02 | (-0.05, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

**Figure R.5.2.1: 5**

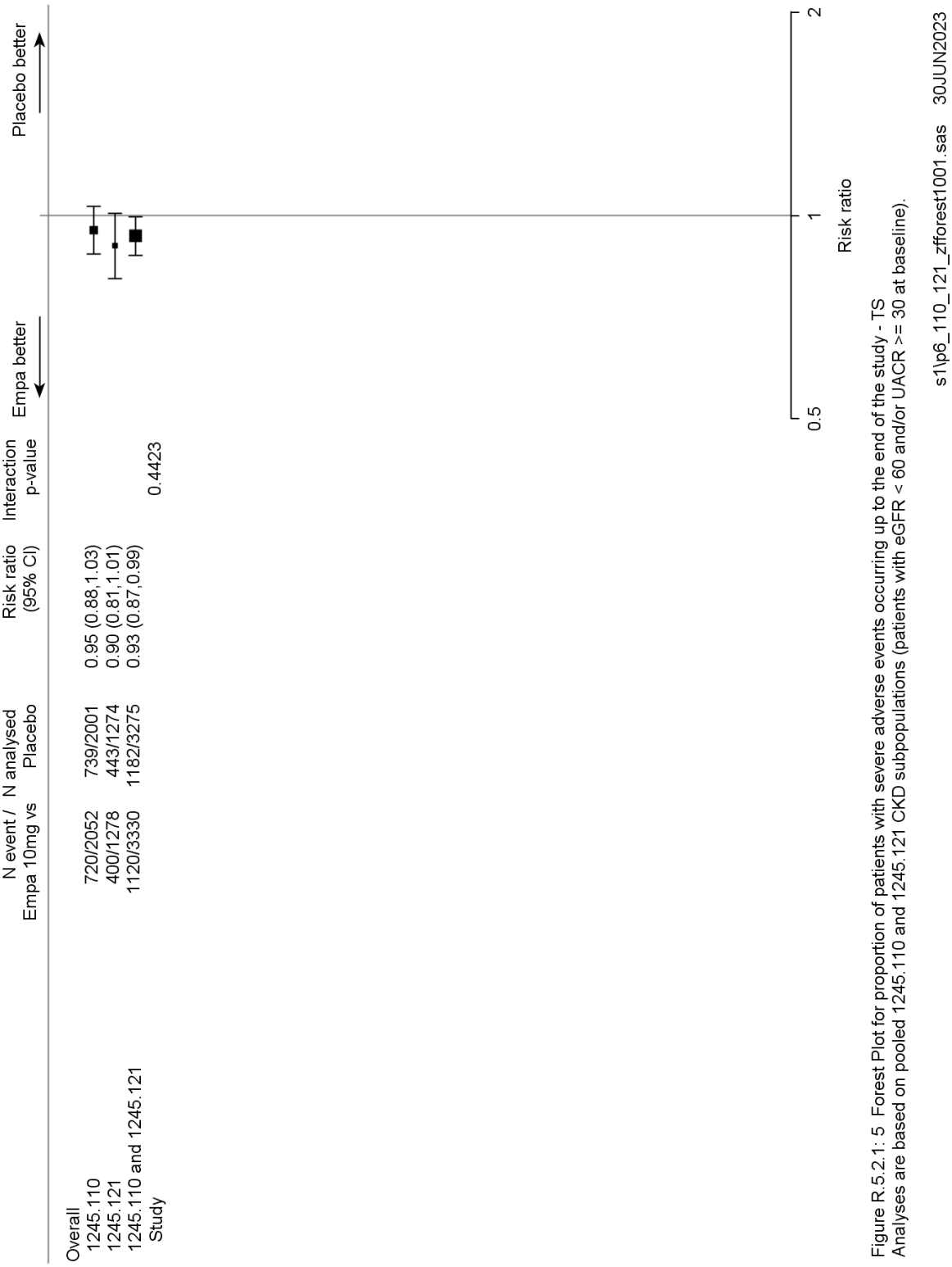


Figure R.5.2.1: 5 Forest Plot for proportion of patients with severe adverse events occurring up to the end of the study - TS
Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.2.1: 5 Proportion of patients with severe adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 1182 | 36.1 | 3330 | 1120 | 33.6 | 0.0349 | 0.93 | (0.87, 0.99) | 0.90 | (0.81,0.99) | -0.02 | (-0.05, 0.00) | |
| Study | | | | | | | | | | | | | | 0.4423 |
| 1245.110 | 2001 | 739 | 36.9 | 2052 | 720 | 35.1 | 0.2215 | 0.95 | (0.88, 1.03) | 0.92 | (0.81,1.05) | -0.02 | (-0.05, 0.01) | |
| 1245.121 | 1274 | 443 | 34.8 | 1278 | 400 | 31.3 | 0.0622 | 0.90 | (0.81, 1.01) | 0.85 | (0.72,1.01) | -0.03 | (-0.07, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.5599 |
| Male | 2023 | 760 | 37.6 | 2068 | 734 | 35.5 | 0.1660 | 0.94 | (0.87, 1.02) | 0.91 | (0.80,1.04) | -0.02 | (-0.05, 0.01) | |
| Female | 1252 | 422 | 33.7 | 1262 | 386 | 30.6 | 0.0893 | 0.91 | (0.81, 1.02) | 0.86 | (0.73,1.02) | -0.03 | (-0.07, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.8652 |
| <65 | 766 | 270 | 35.2 | 705 | 229 | 32.5 | 0.2607 | 0.92 | (0.80, 1.06) | 0.88 | (0.71,1.10) | -0.03 | (-0.08, 0.02) | |
| >=65 | 2509 | 912 | 36.3 | 2625 | 891 | 33.9 | 0.0721 | 0.93 | (0.87, 1.01) | 0.90 | (0.80,1.01) | -0.02 | (-0.05, 0.00) | |
| Region | | | | | | | | | | | | | | 0.6156 |
| North America | 434 | 201 | 46.3 | 432 | 204 | 47.2 | 0.7919 | 1.02 | (0.88, 1.17) | 1.04 | (0.79,1.35) | 0.01 | (-0.06, 0.08) | |
| Latin America | 931 | 351 | 37.7 | 944 | 333 | 35.3 | 0.2943 | 0.94 | (0.83, 1.06) | 0.90 | (0.75,1.09) | -0.02 | (-0.07, 0.02) | |
| Europe | 1334 | 425 | 31.9 | 1361 | 402 | 29.5 | 0.1914 | 0.93 | (0.83, 1.04) | 0.90 | (0.76,1.06) | -0.02 | (-0.06, 0.01) | |
| Asia | 405 | 138 | 34.1 | 413 | 119 | 28.8 | 0.1099 | 0.85 | (0.69, 1.04) | 0.79 | (0.58,1.06) | -0.05 | (-0.12, 0.01) | |
| Other | 171 | 67 | 39.2 | 180 | 62 | 34.4 | 0.2922 | 0.86 | (0.66, 1.13) | 0.79 | (0.51,1.23) | -0.05 | (-0.15, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8222 |
| Diabetic | 1739 | 676 | 38.9 | 1779 | 640 | 36.0 | 0.0733 | 0.92 | (0.85, 1.01) | 0.88 | (0.77,1.01) | -0.03 | (-0.06, 0.00) | |
| Non-Diabetic | 1536 | 506 | 32.9 | 1551 | 480 | 30.9 | 0.2324 | 0.94 | (0.85, 1.04) | 0.91 | (0.78,1.06) | -0.02 | (-0.05, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0567 |
| <30 | 1975 | 726 | 36.8 | 1930 | 627 | 32.5 | 0.0044 | 0.88 | (0.81, 0.96) | 0.83 | (0.72,0.94) | -0.04 | (-0.07,-0.01) | |
| >=30 | 1300 | 456 | 35.1 | 1400 | 493 | 35.2 | 0.9218 | 1.01 | (0.91, 1.11) | 1.01 | (0.86,1.18) | 0.00 | (-0.03, 0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6108 |
| <130 | 1684 | 620 | 36.8 | 1687 | 570 | 33.8 | 0.0622 | 0.92 | (0.84,>1.00) | 0.87 | (0.76,1.01) | -0.03 | (-0.06, 0.00) | |
| >=130 | 1591 | 562 | 35.3 | 1643 | 550 | 33.5 | 0.2775 | 0.95 | (0.86, 1.04) | 0.92 | (0.80,1.07) | -0.02 | (-0.05, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.1: 5 Proportion of patients with severe adverse events occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9774 |
| <75 | 1653 | 629 | 38.1 | 1612 | 577 | 35.8 | 0.1739 | 0.94 | (0.86, 1.03) | 0.91 | (0.79,1.04) | -0.02 | (-0.06, 0.01) | |
| 75 to <85 | 1005 | 349 | 34.7 | 1085 | 348 | 32.1 | 0.2036 | 0.92 | (0.82, 1.04) | 0.89 | (0.74,1.07) | -0.03 | (-0.07, 0.01) | |
| >=85 | 617 | 204 | 33.1 | 633 | 195 | 30.8 | 0.3945 | 0.93 | (0.79, 1.10) | 0.90 | (0.71,1.14) | -0.02 | (-0.07, 0.03) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9253 |
| <30 | 250 | 139 | 55.6 | 263 | 132 | 50.2 | 0.3312 | 0.92 | (0.78, 1.09) | 0.84 | (0.59,1.19) | -0.04 | (-0.13, 0.04) | |
| 30 to <45 | 898 | 351 | 39.1 | 909 | 326 | 35.9 | 0.1495 | 0.92 | (0.81, 1.03) | 0.87 | (0.72,1.05) | -0.03 | (-0.08, 0.01) | |
| >=45 | 2126 | 692 | 32.5 | 2158 | 662 | 30.7 | 0.1871 | 0.94 | (0.86, 1.03) | 0.92 | (0.81,1.04) | -0.02 | (-0.05, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9513 |
| Normal (<30) | 1216 | 373 | 30.7 | 1243 | 352 | 28.3 | 0.1973 | 0.92 | (0.82, 1.04) | 0.89 | (0.75,1.06) | -0.02 | (-0.06, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 576 | 37.2 | 1546 | 541 | 35.0 | 0.1921 | 0.94 | (0.86, 1.03) | 0.91 | (0.78,1.05) | -0.02 | (-0.06, 0.01) | |
| Macroalbuminuria (>300) | 500 | 227 | 45.4 | 525 | 226 | 43.0 | 0.4615 | 0.95 | (0.83, 1.09) | 0.91 | (0.71,1.17) | -0.02 | (-0.08, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8214 |
| Low, moderate or high | 2430 | 784 | 32.3 | 2495 | 754 | 30.2 | 0.1197 | 0.94 | (0.86, 1.02) | 0.91 | (0.81,1.03) | -0.02 | (-0.05, 0.01) | |
| Very high | 834 | 393 | 47.1 | 820 | 366 | 44.6 | 0.3433 | 0.95 | (0.86, 1.06) | 0.91 | (0.75,1.11) | -0.02 | (-0.07, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1072 |
| No | 572 | 228 | 39.9 | 578 | 238 | 41.2 | 0.6404 | 1.03 | (0.90, 1.19) | 1.06 | (0.84,1.34) | 0.01 | (-0.04, 0.07) | |
| Yes | 2703 | 954 | 35.3 | 2752 | 882 | 32.0 | 0.0108 | 0.91 | (0.84, 0.98) | 0.86 | (0.77,0.97) | -0.03 | (-0.06,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8428 |
| No | 344 | 136 | 39.5 | 349 | 131 | 37.5 | 0.5784 | 0.95 | (0.79, 1.14) | 0.92 | (0.67,1.25) | -0.02 | (-0.09, 0.05) | |
| Yes | 2931 | 1046 | 35.7 | 2981 | 989 | 33.2 | 0.0400 | 0.93 | (0.87,<1.00) | 0.89 | (0.80,0.99) | -0.03 | (-0.05, 0.00) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3432 |
| No | 275 | 84 | 30.5 | 307 | 77 | 25.1 | 0.1543 | 0.83 | (0.64, 1.07) | 0.77 | (0.53,1.10) | -0.05 | (-0.13, 0.02) | |
| Yes | 3000 | 1098 | 36.6 | 3023 | 1043 | 34.5 | 0.0862 | 0.94 | (0.88, 1.01) | 0.91 | (0.82,1.01) | -0.02 | (-0.05, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

**Figure R.5.2.1: 6**

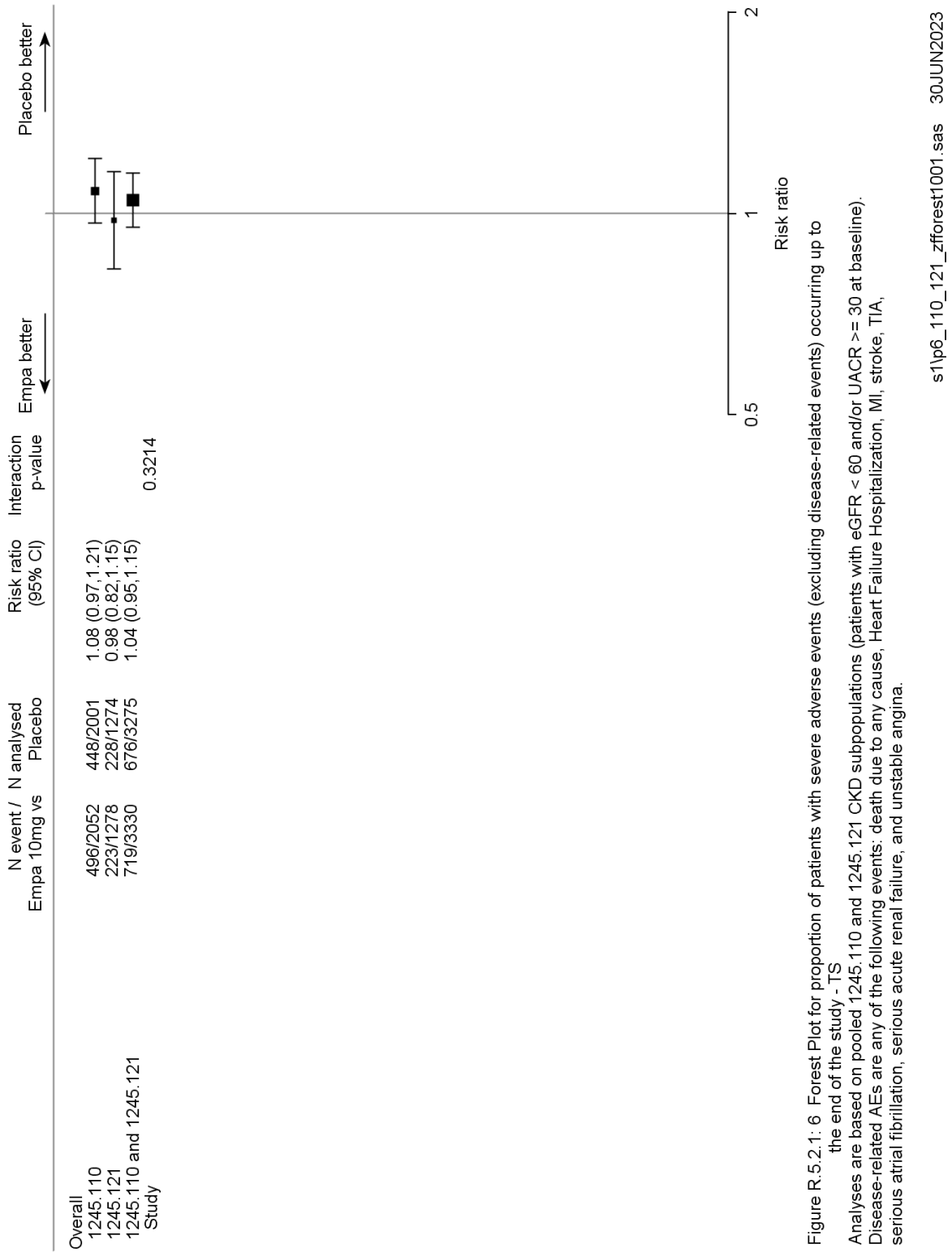


Figure R.5.2.1: 6 Forest Plot for proportion of patients with severe adverse events (excluding disease-related events) occurring up to the end of the study - TS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.

Table R.5.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 676 | 20.6 | 3330 | 719 | 21.6 | 0.3582 | 1.04 | (0.95,1.15) | 1.06 | (0.94,1.19) | 0.01 | (-0.01,0.03) | |
| Study | | | | | | | | | | | | | | 0.3214 |
| 1245.110 | 2001 | 448 | 22.4 | 2052 | 496 | 24.2 | 0.1795 | 1.08 | (0.97,1.21) | 1.11 | (0.96,1.28) | 0.02 | (-0.01,0.04) | |
| 1245.121 | 1274 | 228 | 17.9 | 1278 | 223 | 17.4 | 0.7671 | 0.98 | (0.82,1.15) | 0.97 | (0.79,1.19) | 0.00 | (-0.03,0.03) | |
| Sex | | | | | | | | | | | | | | 0.8539 |
| Male | 2023 | 428 | 21.2 | 2068 | 460 | 22.2 | 0.4034 | 1.05 | (0.94,1.18) | 1.07 | (0.92,1.24) | 0.01 | (-0.01,0.04) | |
| Female | 1252 | 248 | 19.8 | 1262 | 259 | 20.5 | 0.6928 | 1.03 | (0.88,1.21) | 1.04 | (0.86,1.26) | 0.01 | (-0.02,0.04) | |
| Age [years] | | | | | | | | | | | | | | 0.9721 |
| <65 | 766 | 152 | 19.8 | 705 | 147 | 20.9 | 0.6459 | 1.05 | (0.86,1.28) | 1.06 | (0.82,1.37) | 0.01 | (-0.03,0.05) | |
| >=65 | 2509 | 524 | 20.9 | 2625 | 572 | 21.8 | 0.4174 | 1.04 | (0.94,1.16) | 1.06 | (0.92,1.21) | 0.01 | (-0.01,0.03) | |
| Region | | | | | | | | | | | | | | 0.3328 |
| North America | 434 | 142 | 32.7 | 432 | 158 | 36.6 | 0.2350 | 1.12 | (0.93,1.34) | 1.19 | (0.90,1.57) | 0.04 | (-0.02,0.10) | |
| Latin America | 931 | 197 | 21.2 | 944 | 199 | 21.1 | 0.9796 | 1.00 | (0.84,1.19) | 1.00 | (0.80,1.25) | 0.00 | (-0.04,0.04) | |
| Europe | 1334 | 223 | 16.7 | 1361 | 257 | 18.9 | 0.1454 | 1.13 | (0.96,1.33) | 1.16 | (0.95,1.41) | 0.02 | (-0.01,0.05) | |
| Asia | 405 | 76 | 18.8 | 413 | 62 | 15.0 | 0.1435 | 0.80 | (0.58,1.08) | 0.76 | (0.53,1.10) | -0.04 | (-0.09,0.01) | |
| Other | 171 | 38 | 22.2 | 180 | 43 | 23.9 | 0.8084 | 1.05 | (0.72,1.52) | 1.06 | (0.64,1.77) | 0.01 | (-0.08,0.10) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7154 |
| Diabetic | 1739 | 383 | 22.0 | 1779 | 416 | 23.4 | 0.3502 | 1.06 | (0.94,1.20) | 1.08 | (0.92,1.26) | 0.01 | (-0.01,0.04) | |
| Non-Diabetic | 1536 | 293 | 19.1 | 1551 | 303 | 19.5 | 0.7551 | 1.02 | (0.89,1.18) | 1.03 | (0.86,1.23) | 0.00 | (-0.02,0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0933 |
| <30 | 1975 | 394 | 19.9 | 1930 | 375 | 19.4 | 0.6369 | 0.97 | (0.85,1.10) | 0.96 | (0.82,1.13) | -0.01 | (-0.03,0.02) | |
| >=30 | 1300 | 282 | 21.7 | 1400 | 344 | 24.6 | 0.0646 | 1.14 | (0.99,1.31) | 1.18 | (0.99,1.42) | 0.03 | ( 0.00,0.06) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7680 |
| <130 | 1684 | 351 | 20.8 | 1687 | 364 | 21.6 | 0.6481 | 1.03 | (0.91,1.17) | 1.04 | (0.88,1.23) | 0.01 | (-0.02,0.03) | |
| >=130 | 1591 | 325 | 20.4 | 1643 | 355 | 21.6 | 0.3922 | 1.06 | (0.93,1.21) | 1.08 | (0.91,1.28) | 0.01 | (-0.02,0.04) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9563 |
| <75 | 1653 | 354 | 21.4 | 1612 | 366 | 22.7 | 0.4065 | 1.06 | (0.93,1.20) | 1.07 | (0.91,1.27) | 0.01 | (-0.02,0.04) | |
| 75 to <85 | 1005 | 201 | 20.0 | 1085 | 227 | 20.9 | 0.5831 | 1.05 | (0.89,1.24) | 1.06 | (0.86,1.31) | 0.01 | (-0.02,0.04) | |
| >=85 | 617 | 121 | 19.6 | 633 | 126 | 19.9 | 0.8933 | 1.02 | (0.81,1.27) | 1.02 | (0.77,1.35) | 0.00 | (-0.04,0.05) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6841 |
| <30 | 250 | 90 | 36.0 | 263 | 93 | 35.4 | 0.8472 | 1.02 | (0.81,1.29) | 1.04 | (0.72,1.50) | 0.01 | (-0.07,0.09) | |
| 30 to <45 | 898 | 203 | 22.6 | 909 | 204 | 22.4 | 0.8997 | 0.99 | (0.83,1.17) | 0.99 | (0.79,1.23) | 0.00 | (-0.04,0.04) | |
| >=45 | 2126 | 383 | 18.0 | 2158 | 422 | 19.6 | 0.2067 | 1.08 | (0.96,1.23) | 1.10 | (0.95,1.29) | 0.02 | (-0.01,0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2773 |
| Normal (<30) | 1216 | 233 | 19.2 | 1243 | 236 | 19.0 | 0.8996 | 0.99 | (0.84,1.16) | 0.99 | (0.81,1.21) | 0.00 | (-0.03,0.03) | |
| Microalbuminuria (30 to <=300) | 1548 | 306 | 19.8 | 1546 | 348 | 22.5 | 0.0683 | 1.13 | (0.99,1.30) | 1.17 | (0.99,1.40) | 0.03 | ( 0.00,0.06) | |
| Macroalbuminuria (>300) | 500 | 134 | 26.8 | 525 | 134 | 25.5 | 0.6656 | 0.96 | (0.78,1.17) | 0.94 | (0.71,1.24) | -0.01 | (-0.07,0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9087 |
| Low, moderate or high | 2430 | 445 | 18.3 | 2495 | 485 | 19.4 | 0.3335 | 1.06 | (0.94,1.19) | 1.07 | (0.93,1.24) | 0.01 | (-0.01,0.03) | |
| Very high | 834 | 229 | 27.5 | 820 | 234 | 28.5 | 0.5583 | 1.05 | (0.90,1.22) | 1.07 | (0.86,1.32) | 0.01 | (-0.03,0.06) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2024 |
| No | 572 | 140 | 24.5 | 578 | 165 | 28.5 | 0.1121 | 1.17 | (0.96,1.42) | 1.24 | (0.95,1.61) | 0.04 | (-0.01,0.09) | |
| Yes | 2703 | 536 | 19.8 | 2752 | 554 | 20.1 | 0.8104 | 1.01 | (0.91,1.13) | 1.02 | (0.89,1.16) | 0.00 | (-0.02,0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9544 |
| No | 344 | 81 | 23.5 | 349 | 85 | 24.4 | 0.7911 | 1.04 | (0.80,1.35) | 1.05 | (0.74,1.49) | 0.01 | (-0.06,0.07) | |
| Yes | 2931 | 595 | 20.3 | 2981 | 634 | 21.3 | 0.3841 | 1.05 | (0.95,1.15) | 1.06 | (0.93,1.20) | 0.01 | (-0.01,0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.1: 6 Proportion of patients with severe adverse events (excluding disease-related events) occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6279 |
| No | 275 | 47 | 17.1 | 307 | 50 | 16.3 | 0.8282 | 0.96 | (0.67,1.38) | 0.95 | (0.62,1.48) | -0.01 | (-0.07,0.05) | |
| Yes | 3000 | 629 | 21.0 | 3023 | 669 | 22.1 | 0.2847 | 1.05 | (0.96,1.16) | 1.07 | (0.95,1.21) | 0.01 | (-0.01,0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Disease-related AEs are any of the following events: death due to any cause, Heart Failure Hospitalization, MI, stroke, TIA, serious atrial fibrillation, serious acute renal failure, and unstable angina.
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

**R.5.2.2**

R.5.2.2 Adverse events leading to treatment discontinuation

**Figure R.5.2.2: 1**

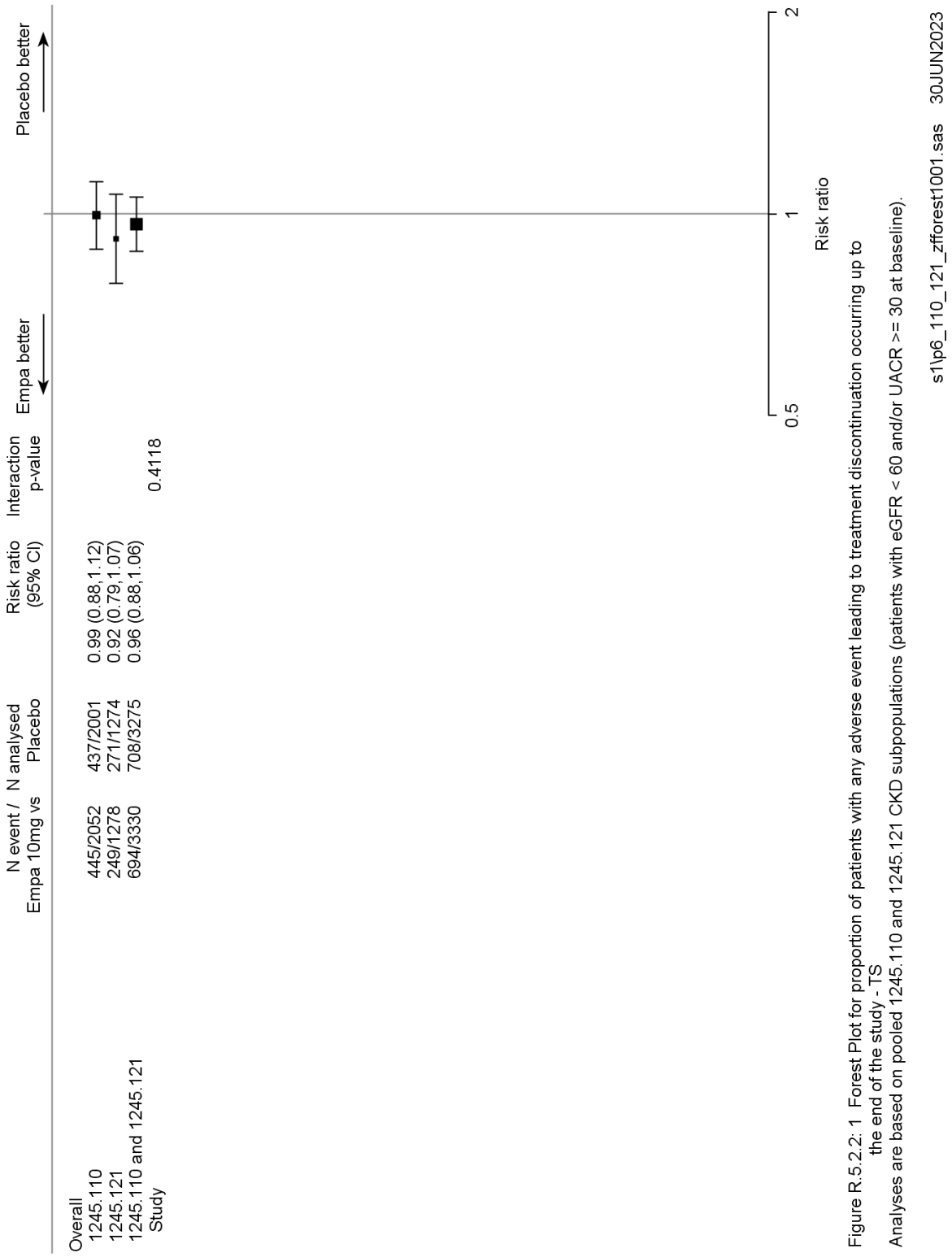


Figure R.5.2.2: 1 Forest Plot for proportion of patients with any adverse event leading to treatment discontinuation occurring up to the end of the study - TS

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).

Table R.5.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation occurring up to the end of the study, overall and by subgroup - TS

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 708 | 21.6 | 3330 | 694 | 20.8 | 0.4355 | 0.96 | (0.88,1.06) | 0.95 | (0.85,1.07) | -0.01 | (-0.03,0.01) | |
| Study | | | | | | | | | | | | | | 0.4118 |
| 1245.110 | 2001 | 437 | 21.8 | 2052 | 445 | 21.7 | 0.9061 | 0.99 | (0.88,1.12) | 0.99 | (0.85,1.15) | 0.00 | (-0.03,0.02) | |
| 1245.121 | 1274 | 271 | 21.3 | 1278 | 249 | 19.5 | 0.2623 | 0.92 | (0.79,1.07) | 0.90 | (0.74,1.09) | -0.02 | (-0.05,0.01) | |
| Sex | | | | | | | | | | | | | | 0.7545 |
| Male | 2023 | 454 | 22.4 | 2068 | 452 | 21.9 | 0.6500 | 0.97 | (0.87,1.09) | 0.97 | (0.83,1.12) | -0.01 | (-0.03,0.02) | |
| Female | 1252 | 254 | 20.3 | 1262 | 242 | 19.2 | 0.4733 | 0.94 | (0.81,1.11) | 0.93 | (0.76,1.13) | -0.01 | (-0.04,0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.5024 |
| <65 | 766 | 154 | 20.1 | 705 | 128 | 18.2 | 0.3327 | 0.90 | (0.73,1.11) | 0.88 | (0.68,1.14) | -0.02 | (-0.06,0.02) | |
| >=65 | 2509 | 554 | 22.1 | 2625 | 566 | 21.6 | 0.6533 | 0.98 | (0.88,1.08) | 0.97 | (0.85,1.11) | -0.01 | (-0.03,0.02) | |
| Region | | | | | | | | | | | | | | 0.6789 |
| North America | 434 | 108 | 24.9 | 432 | 112 | 25.9 | 0.7253 | 1.04 | (0.83,1.31) | 1.06 | (0.78,1.43) | 0.01 | (-0.05,0.07) | |
| Latin America | 931 | 217 | 23.3 | 944 | 199 | 21.1 | 0.2604 | 0.91 | (0.77,1.07) | 0.88 | (0.71,1.10) | -0.02 | (-0.06,0.02) | |
| Europe | 1334 | 287 | 21.5 | 1361 | 279 | 20.5 | 0.5240 | 0.95 | (0.82,1.10) | 0.94 | (0.78,1.13) | -0.01 | (-0.04,0.02) | |
| Asia | 405 | 53 | 13.1 | 413 | 63 | 15.3 | 0.3782 | 1.16 | (0.83,1.63) | 1.19 | (0.80,1.77) | 0.02 | (-0.03,0.07) | |
| Other | 171 | 43 | 25.1 | 180 | 41 | 22.8 | 0.5534 | 0.89 | (0.61,1.30) | 0.86 | (0.53,1.41) | -0.03 | (-0.12,0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6467 |
| Diabetic | 1739 | 391 | 22.5 | 1779 | 378 | 21.2 | 0.3723 | 0.94 | (0.83,1.07) | 0.93 | (0.79,1.09) | -0.01 | (-0.04,0.01) | |
| Non-Diabetic | 1536 | 317 | 20.6 | 1551 | 316 | 20.4 | 0.8523 | 0.99 | (0.86,1.13) | 0.98 | (0.83,1.17) | 0.00 | (-0.03,0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1020 |
| <30 | 1975 | 447 | 22.6 | 1930 | 396 | 20.5 | 0.1027 | 0.91 | (0.80,1.02) | 0.88 | (0.76,1.03) | -0.02 | (-0.05,0.00) | |
| >=30 | 1300 | 261 | 20.1 | 1400 | 298 | 21.3 | 0.4332 | 1.06 | (0.91,1.23) | 1.08 | (0.89,1.30) | 0.01 | (-0.02,0.04) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4249 |
| <130 | 1684 | 357 | 21.2 | 1687 | 358 | 21.2 | 0.9816 | 1.00 | (0.88,1.14) | 1.00 | (0.85,1.18) | 0.00 | (-0.03,0.03) | |
| >=130 | 1591 | 351 | 22.1 | 1643 | 336 | 20.5 | 0.2731 | 0.93 | (0.81,1.06) | 0.91 | (0.77,1.08) | -0.02 | (-0.04,0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.2: 1 Proportion of patients with any adverse event leading to treatment discontinuation occurring up to the end of the study, overall and by subgroup - TS

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4335 |
| <75 | 1653 | 382 | 23.1 | 1612 | 353 | 21.9 | 0.4140 | 0.95 | (0.83,1.08) | 0.93 | (0.79,1.10) | -0.01 | (-0.04,0.02) | |
| 75 to <85 | 1005 | 198 | 19.7 | 1085 | 225 | 20.7 | 0.5449 | 1.05 | (0.89,1.25) | 1.07 | (0.86,1.32) | 0.01 | (-0.02,0.05) | |
| >=85 | 617 | 128 | 20.7 | 633 | 116 | 18.3 | 0.2865 | 0.88 | (0.71,1.11) | 0.86 | (0.65,1.14) | -0.02 | (-0.07,0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6551 |
| <30 | 250 | 90 | 36.0 | 263 | 84 | 31.9 | 0.3898 | 0.90 | (0.70,1.15) | 0.85 | (0.59,1.23) | -0.04 | (-0.12,0.05) | |
| 30 to <45 | 898 | 205 | 22.8 | 909 | 212 | 23.3 | 0.8011 | 1.02 | (0.86,1.21) | 1.03 | (0.83,1.28) | 0.00 | (-0.03,0.04) | |
| >=45 | 2126 | 413 | 19.4 | 2158 | 398 | 18.4 | 0.3990 | 0.95 | (0.84,1.07) | 0.94 | (0.80,1.09) | -0.01 | (-0.03,0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9854 |
| Normal (<30) | 1216 | 220 | 18.1 | 1243 | 218 | 17.5 | 0.7207 | 0.97 | (0.82,1.15) | 0.96 | (0.78,1.18) | -0.01 | (-0.04,0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 344 | 22.2 | 1546 | 331 | 21.4 | 0.5746 | 0.96 | (0.84,1.10) | 0.95 | (0.80,1.13) | -0.01 | (-0.04,0.02) | |
| Macroalbuminuria (>300) | 500 | 140 | 28.0 | 525 | 144 | 27.4 | 0.8637 | 0.98 | (0.81,1.20) | 0.98 | (0.74,1.28) | 0.00 | (-0.06,0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3379 |
| Low, moderate or high | 2430 | 466 | 19.2 | 2495 | 452 | 18.1 | 0.3343 | 0.94 | (0.84,1.06) | 0.93 | (0.81,1.08) | -0.01 | (-0.03,0.01) | |
| Very high | 834 | 238 | 28.5 | 820 | 242 | 29.5 | 0.6426 | 1.04 | (0.89,1.20) | 1.05 | (0.85,1.30) | 0.01 | (-0.03,0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7805 |
| No | 572 | 140 | 24.5 | 578 | 140 | 24.2 | 0.9153 | 0.99 | (0.81,1.21) | 0.99 | (0.75,1.29) | 0.00 | (-0.05,0.05) | |
| Yes | 2703 | 568 | 21.0 | 2752 | 554 | 20.1 | 0.4128 | 0.96 | (0.86,1.06) | 0.95 | (0.83,1.08) | -0.01 | (-0.03,0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5582 |
| No | 344 | 90 | 26.2 | 349 | 82 | 23.5 | 0.4052 | 0.90 | (0.69,1.16) | 0.86 | (0.61,1.22) | -0.03 | (-0.09,0.04) | |
| Yes | 2931 | 618 | 21.1 | 2981 | 612 | 20.5 | 0.5914 | 0.97 | (0.88,1.07) | 0.97 | (0.85,1.10) | -0.01 | (-0.03,0.02) | |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2275 |
| No | 275 | 57 | 20.7 | 307 | 50 | 16.3 | 0.1719 | 0.79 | (0.56,1.11) | 0.75 | (0.49,1.14) | -0.04 | (-0.11,0.02) | |
| Yes | 3000 | 651 | 21.7 | 3023 | 644 | 21.3 | 0.7017 | 0.98 | (0.89,1.08) | 0.98 | (0.86,1.10) | 0.00 | (-0.02,0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
For risk ratios, odds ratios and risk differences, asymptotic confidence limits are calculated.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Number of patients | 3275 (100.0) | | | 3330 (100.0) | | |
| Total with adverse events | 708 ( 21.6) | 5644.50 | 12.54 | 694 ( 20.8) | 5773.39 | 12.02 |
| Cardiac disorders | 211 ( 6.4) | 5959.29 | 3.54 | 177 ( 5.3) | 6095.16 | 2.90 |
| Cardiac failure | 117 ( 3.6) | 5975.61 | 1.96 | 90 ( 2.7) | 6116.90 | 1.47 |
| Cardiac failure congestive | 14 ( 0.4) | 6014.56 | 0.23 | 10 ( 0.3) | 6136.31 | 0.16 |
| Myocardial infarction | 14 ( 0.4) | 6019.53 | 0.23 | 11 ( 0.3) | 6141.32 | 0.18 |
| Acute myocardial infarction | 13 ( 0.4) | 6019.14 | 0.22 | 12 ( 0.4) | 6140.54 | 0.20 |
| Cardiac arrest | 9 ( 0.3) | 6019.72 | 0.15 | 13 ( 0.4) | 6140.60 | 0.21 |
| Cardiac failure acute | 11 ( 0.3) | 6017.91 | 0.18 | 6 ( 0.2) | 6138.89 | 0.10 |
| Cardiogenic shock | 7 ( 0.2) | 6019.75 | 0.12 | 5 ( 0.2) | 6141.41 | 0.08 |
| Cardiac failure chronic | 4 ( 0.1) | 6019.40 | 0.07 | 2 ( 0.1) | 6141.39 | 0.03 |
| Atrial fibrillation | 1 ( <0.1) | 6019.19 | 0.02 | 4 ( 0.1) | 6140.19 | 0.07 |
| Cardio-respiratory arrest | 3 ( 0.1) | 6019.52 | 0.05 | 3 ( 0.1) | 6141.41 | 0.05 |
| Cardiopulmonary failure | 2 ( 0.1) | 6019.75 | 0.03 | 3 ( 0.1) | 6141.43 | 0.05 |
| Arrhythmia | 2 ( 0.1) | 6017.69 | 0.03 | 0 | 6141.44 | 0 |
| Coronary artery disease | 2 ( 0.1) | 6019.72 | 0.03 | 0 | 6141.44 | 0 |
| Ventricular arrhythmia | 2 ( 0.1) | 6019.75 | 0.03 | 0 | 6141.44 | 0 |
| Acute left ventricular failure | 0 | 6019.75 | 0 | 2 ( 0.1) | 6141.37 | 0.03 |
| Aortic valve incompetence | 0 | 6019.75 | 0 | 2 ( 0.1) | 6140.25 | 0.03 |
| Ventricular fibrillation | 1 ( <0.1) | 6019.74 | 0.02 | 2 ( 0.1) | 6141.44 | 0.03 |
| Angina pectoris | 1 ( <0.1) | 6017.11 | 0.02 | 0 | 6141.44 | 0 |
| Aortic valve stenosis | 1 ( <0.1) | 6019.41 | 0.02 | 0 | 6141.44 | 0 |
| Arrhythmic storm | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Bradycardia | 1 ( <0.1) | 6019.05 | 0.02 | 0 | 6141.44 | 0 |
| Congestive cardiomyopathy | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Left ventricular dysfunction | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Myocarditis | 1 ( <0.1) | 6019.73 | 0.02 | 0 | 6141.44 | 0 |
| Tachycardia | 1 ( <0.1) | 6018.55 | 0.02 | 1 ( <0.1) | 6138.97 | 0.02 |
| Ventricular tachycardia | 1 ( <0.1) | 6019.47 | 0.02 | 1 ( <0.1) | 6141.39 | 0.02 |
| Angina unstable | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.42 | 0.02 |
| Atrial tachycardia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.26 | 0.02 |
| Atrioventricular block complete | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.22 | 0.02 |
| Atrioventricular block second degree | 0 | 6019.75 | 0 | 1 ( <0.1) | 6137.96 | 0.02 |
| Cardiac tamponade | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.44 | 0.02 |
| Chronic left ventricular failure | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.04 | 0.02 |
| Ischaemic cardiomyopathy | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.44 | 0.02 |
| Mitral valve incompetence | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.41 | 0.02 |
| Paroxysmal atrioventricular block | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.34 | 0.02 |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version: 25.0

Table R.5.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Cardiac disorders (cont.) | | | | | | |
| Sinus node dysfunction | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.77 | 0.02 |
| Infections and infestations | 81 ( 2.5) | 5991.73 | 1.35 | 104 ( 3.1) | 6092.43 | 1.71 |
| Urinary tract infection | 10 ( 0.3) | 6009.06 | 0.17 | 17 ( 0.5) | 6124.81 | 0.28 |
| Pneumonia | 16 ( 0.5) | 6016.12 | 0.27 | 15 ( 0.5) | 6140.19 | 0.24 |
| COVID-19 | 14 ( 0.4) | 6018.01 | 0.23 | 12 ( 0.4) | 6139.77 | 0.20 |
| Sepsis | 7 ( 0.2) | 6019.56 | 0.12 | 10 ( 0.3) | 6140.96 | 0.16 |
| COVID-19 pneumonia | 4 ( 0.1) | 6019.65 | 0.07 | 9 ( 0.3) | 6140.94 | 0.15 |
| Septic shock | 6 ( 0.2) | 6019.58 | 0.10 | 8 ( 0.2) | 6140.02 | 0.13 |
| Urosepsis | 5 ( 0.2) | 6017.13 | 0.08 | 3 ( 0.1) | 6136.94 | 0.05 |
| Pneumonia aspiration | 0 | 6019.75 | 0 | 3 ( 0.1) | 6141.07 | 0.05 |
| Bronchitis | 2 ( 0.1) | 6017.35 | 0.03 | 1 ( <0.1) | 6141.44 | 0.02 |
| Endocarditis | 2 ( 0.1) | 6019.04 | 0.03 | 2 ( 0.1) | 6138.42 | 0.03 |
| Gastroenteritis | 2 ( 0.1) | 6019.17 | 0.03 | 1 ( <0.1) | 6141.42 | 0.02 |
| Fournier's gangrene | 0 | 6019.75 | 0 | 2 ( 0.1) | 6141.07 | 0.03 |
| Fungal balanitis | 0 | 6019.75 | 0 | 2 ( 0.1) | 6139.65 | 0.03 |
| Anal infection | 1 ( <0.1) | 6019.25 | 0.02 | 1 ( <0.1) | 6141.35 | 0.02 |
| Appendicitis | 1 ( <0.1) | 6019.63 | 0.02 | 1 ( <0.1) | 6141.37 | 0.02 |
| Asymptomatic bacteriuria | 1 ( <0.1) | 6019.59 | 0.02 | 0 | 6141.44 | 0 |
| Cholecystitis infective | 1 ( <0.1) | 6019.73 | 0.02 | 0 | 6141.44 | 0 |
| Clostridium difficile infection | 1 ( <0.1) | 6019.66 | 0.02 | 0 | 6141.44 | 0 |
| Gangrene | 1 ( <0.1) | 6018.57 | 0.02 | 1 ( <0.1) | 6140.35 | 0.02 |
| Hepatitis A | 1 ( <0.1) | 6019.66 | 0.02 | 0 | 6141.44 | 0 |
| Influenza | 1 ( <0.1) | 6019.75 | 0.02 | 1 ( <0.1) | 6139.47 | 0.02 |
| Liver abscess | 1 ( <0.1) | 6017.81 | 0.02 | 0 | 6141.44 | 0 |
| Localised infection | 1 ( <0.1) | 6019.03 | 0.02 | 0 | 6141.44 | 0 |
| Peritonsillitis | 1 ( <0.1) | 6019.73 | 0.02 | 0 | 6141.44 | 0 |
| Pneumonia viral | 1 ( <0.1) | 6019.49 | 0.02 | 0 | 6141.44 | 0 |
| Tracheobronchitis | 1 ( <0.1) | 6019.72 | 0.02 | 0 | 6141.44 | 0 |
| Vulvovaginal candidiasis | 1 ( <0.1) | 6019.46 | 0.02 | 1 ( <0.1) | 6138.75 | 0.02 |
| Atypical pneumonia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.37 | 0.02 |
| Balanitis candida | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.04 | 0.02 |
| Cellulitis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.32 | 0.02 |
| Cholangitis infective | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.33 | 0.02 |
| Chronic sinusitis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.53 | 0.02 |
| Device related infection | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.36 | 0.02 |
| Diverticulitis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.29 | 0.02 |
| Escherichia bacteraemia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.26 | 0.02 |
| Genital infection | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.34 | 0.02 |

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MedDRA version: 25.0

Table R.5.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Infections and infestations (cont.) | | | | | | |
| Labyrinthitis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.28 | 0.02 |
| Lung abscess | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.35 | 0.02 |
| Penile infection | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.44 | 0.02 |
| Periodontitis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6139.53 | 0.02 |
| Postoperative abscess | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.16 | 0.02 |
| Pyelonephritis acute | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.43 | 0.02 |
| Small intestine gangrene | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.43 | 0.02 |
| Spontaneous bacterial peritonitis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.40 | 0.02 |
| Vulvovaginal mycotic infection | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.81 | 0.02 |
| General disorders and administration site conditions | 90 ( 2.7) | 5995.69 | 1.50 | 93 ( 2.8) | 6123.23 | 1.52 |
| Death | 41 ( 1.3) | 6019.56 | 0.68 | 54 ( 1.6) | 6140.52 | 0.88 |
| Sudden cardiac death | 15 ( 0.5) | 6019.75 | 0.25 | 8 ( 0.2) | 6141.44 | 0.13 |
| Sudden death | 10 ( 0.3) | 6019.75 | 0.17 | 9 ( 0.3) | 6141.44 | 0.15 |
| Cardiac death | 8 ( 0.2) | 6019.75 | 0.13 | 8 ( 0.2) | 6141.44 | 0.13 |
| Asthenia | 2 ( 0.1) | 6016.55 | 0.03 | 4 ( 0.1) | 6132.52 | 0.07 |
| Fatigue | 2 ( 0.1) | 6013.72 | 0.03 | 4 ( 0.1) | 6135.36 | 0.07 |
| Feeling cold | 2 ( 0.1) | 6014.68 | 0.03 | 0 | 6141.44 | 0 |
| Malaise | 2 ( 0.1) | 6018.48 | 0.03 | 1 ( <0.1) | 6140.90 | 0.02 |
| Multiple organ dysfunction syndrome | 2 ( 0.1) | 6019.74 | 0.03 | 1 ( <0.1) | 6141.44 | 0.02 |
| Oedema peripheral | 2 ( 0.1) | 6014.94 | 0.03 | 0 | 6141.44 | 0 |
| Chest pain | 1 ( <0.1) | 6017.79 | 0.02 | 0 | 6141.44 | 0 |
| Physical deconditioning | 1 ( <0.1) | 6019.64 | 0.02 | 0 | 6141.44 | 0 |
| Vascular stent occlusion | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Vessel puncture site reaction | 1 ( <0.1) | 6018.35 | 0.02 | 0 | 6141.44 | 0 |
| Accidental death | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.44 | 0.02 |
| Non-cardiac chest pain | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.43 | 0.02 |
| Pain | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.65 | 0.02 |
| Peripheral swelling | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.48 | 0.02 |

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Table R.5.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Renal and urinary disorders | 81 ( 2.5) | 5935.59 | 1.36 | 79 ( 2.4) | 6060.10 | 1.30 |
| Renal impairment | 23 ( 0.7) | 5990.25 | 0.38 | 30 ( 0.9) | 6107.16 | 0.49 |
| Acute kidney injury | 17 ( 0.5) | 6007.74 | 0.28 | 15 ( 0.5) | 6130.78 | 0.24 |
| Chronic kidney disease | 15 ( 0.5) | 6004.57 | 0.25 | 15 ( 0.5) | 6126.71 | 0.24 |
| Renal failure | 15 ( 0.5) | 6010.78 | 0.25 | 7 ( 0.2) | 6135.18 | 0.11 |
| Nocturia | 2 ( 0.1) | 6015.68 | 0.03 | 0 | 6141.44 | 0 |
| Urinary incontinence | 2 ( 0.1) | 6016.71 | 0.03 | 2 ( 0.1) | 6137.64 | 0.03 |
| Nephropathy | 0 | 6019.75 | 0 | 2 ( 0.1) | 6140.04 | 0.03 |
| Polyuria | 0 | 6019.75 | 0 | 2 ( 0.1) | 6137.07 | 0.03 |
| Bladder mass | 1 ( <0.1) | 6017.82 | 0.02 | 0 | 6141.44 | 0 |
| Diabetic nephropathy | 1 ( <0.1) | 6018.40 | 0.02 | 1 ( <0.1) | 6141.20 | 0.02 |
| Dysuria | 1 ( <0.1) | 6019.10 | 0.02 | 1 ( <0.1) | 6139.47 | 0.02 |
| End stage renal disease | 1 ( <0.1) | 6018.24 | 0.02 | 0 | 6141.44 | 0 |
| Nephrolithiasis | 1 ( <0.1) | 6017.92 | 0.02 | 1 ( <0.1) | 6140.95 | 0.02 |
| Nephrosclerosis | 1 ( <0.1) | 6017.79 | 0.02 | 0 | 6141.44 | 0 |
| Pollakiuria | 1 ( <0.1) | 6018.57 | 0.02 | 1 ( <0.1) | 6141.33 | 0.02 |
| Renal colic | 1 ( <0.1) | 6017.90 | 0.02 | 0 | 6141.44 | 0 |
| Hypertonic bladder | 0 | 6019.75 | 0 | 1 ( <0.1) | 6138.52 | 0.02 |
| Renal pain | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.31 | 0.02 |

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Table R.5.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Nervous system disorders | 56 ( 1.7) | 5976.27 | 0.94 | 62 ( 1.9) | 6099.83 | 1.02 |
| Ischaemic stroke | 17 ( 0.5) | 6009.51 | 0.28 | 12 ( 0.4) | 6136.82 | 0.20 |
| Dizziness | 10 ( 0.3) | 6002.90 | 0.17 | 4 ( 0.1) | 6133.03 | 0.07 |
| Cerebrovascular accident | 7 ( 0.2) | 6017.92 | 0.12 | 8 ( 0.2) | 6139.63 | 0.13 |
| Syncope | 1 ( <0.1) | 6019.55 | 0.02 | 7 ( 0.2) | 6135.91 | 0.11 |
| Haemorrhagic stroke | 4 ( 0.1) | 6017.91 | 0.07 | 6 ( 0.2) | 6139.06 | 0.10 |
| Dementia | 3 ( 0.1) | 6018.39 | 0.05 | 4 ( 0.1) | 6137.43 | 0.07 |
| Cognitive disorder | 0 | 6019.75 | 0 | 3 ( 0.1) | 6140.19 | 0.05 |
| Cerebral infarction | 2 ( 0.1) | 6018.67 | 0.03 | 1 ( <0.1) | 6141.42 | 0.02 |
| Headache | 2 ( 0.1) | 6015.83 | 0.03 | 0 | 6141.44 | 0 |
| Cerebral haemorrhage | 1 ( <0.1) | 6019.75 | 0.02 | 2 ( 0.1) | 6141.43 | 0.03 |
| Embolic stroke | 0 | 6019.75 | 0 | 2 ( 0.1) | 6140.45 | 0.03 |
| Parkinson’s disease | 0 | 6019.75 | 0 | 2 ( 0.1) | 6139.78 | 0.03 |
| Altered state of consciousness | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Brain injury | 1 ( <0.1) | 6019.73 | 0.02 | 0 | 6141.44 | 0 |
| Cerebral artery embolism | 1 ( <0.1) | 6019.71 | 0.02 | 0 | 6141.44 | 0 |
| Cerebral artery occlusion | 1 ( <0.1) | 6018.67 | 0.02 | 0 | 6141.44 | 0 |
| Cerebral haematoma | 1 ( <0.1) | 6019.74 | 0.02 | 0 | 6141.44 | 0 |
| Embolic cerebral infarction | 1 ( <0.1) | 6016.95 | 0.02 | 0 | 6141.44 | 0 |
| Lethargy | 1 ( <0.1) | 6017.76 | 0.02 | 0 | 6141.44 | 0 |
| Memory impairment | 1 ( <0.1) | 6018.46 | 0.02 | 0 | 6141.44 | 0 |
| Nervous system disorder | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Thalamus haemorrhage | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Cerebellar haematoma | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.95 | 0.02 |
| Cerebral arteriosclerosis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.93 | 0.02 |
| Dementia Alzheimer’s type | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.43 | 0.02 |
| Haemorrhage intracranial | 0 | 6019.75 | 0 | 1 ( <0.1) | 6138.97 | 0.02 |
| Hypoaesthesia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6139.23 | 0.02 |
| Hypoxic-ischaemic encephalopathy | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.42 | 0.02 |
| Intracranial aneurysm | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.21 | 0.02 |
| Postresuscitation encephalopathy | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.37 | 0.02 |
| Sciatica | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.41 | 0.02 |
| Seizure | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.32 | 0.02 |
| Transient ischaemic attack | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.27 | 0.02 |
| Tremor | 0 | 6019.75 | 0 | 1 ( <0.1) | 6138.58 | 0.02 |

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|---|---|---|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 34 ( 1.0) | 5999.95 | 0.57 | 30 ( 0.9) | 6124.88 | 0.49 |
| Lung neoplasm malignant | 3 ( 0.1) | 6018.78 | 0.05 | 2 ( 0.1) | 6140.96 | 0.03 |
| Pancreatic carcinoma | 3 ( 0.1) | 6019.23 | 0.05 | 1 ( <0.1) | 6140.96 | 0.02 |
| Adenocarcinoma pancreas | 2 ( 0.1) | 6018.76 | 0.03 | 0 | 6141.44 | 0 |
| Colon cancer metastatic | 2 ( 0.1) | 6018.49 | 0.03 | 0 | 6141.44 | 0 |
| Lung adenocarcinoma | 2 ( 0.1) | 6018.54 | 0.03 | 1 ( <0.1) | 6140.30 | 0.02 |
| Oesophageal carcinoma | 2 ( 0.1) | 6019.56 | 0.03 | 0 | 6141.44 | 0 |
| Squamous cell carcinoma of lung | 2 ( 0.1) | 6016.38 | 0.03 | 0 | 6141.44 | 0 |
| Transitional cell carcinoma | 0 | 6019.75 | 0 | 2 ( 0.1) | 6139.23 | 0.03 |
| Bladder cancer | 1 ( <0.1) | 6019.70 | 0.02 | 0 | 6141.44 | 0 |
| Bladder transitional cell carcinoma | 1 ( <0.1) | 6019.16 | 0.02 | 0 | 6141.44 | 0 |
| Breast cancer female | 1 ( <0.1) | 6018.51 | 0.02 | 0 | 6141.44 | 0 |
| Colon cancer | 1 ( <0.1) | 6018.69 | 0.02 | 1 ( <0.1) | 6141.42 | 0.02 |
| Gastric neoplasm | 1 ( <0.1) | 6019.61 | 0.02 | 0 | 6141.44 | 0 |
| Hepatocellular carcinoma | 1 ( <0.1) | 6019.51 | 0.02 | 0 | 6141.44 | 0 |
| Laryngeal squamous cell carcinoma | 1 ( <0.1) | 6018.04 | 0.02 | 0 | 6141.44 | 0 |
| Leiomyosarcoma | 1 ( <0.1) | 6019.27 | 0.02 | 0 | 6141.44 | 0 |
| Lung neoplasm | 1 ( <0.1) | 6019.71 | 0.02 | 1 ( <0.1) | 6140.21 | 0.02 |
| Mantle cell lymphoma | 1 ( <0.1) | 6017.39 | 0.02 | 0 | 6141.44 | 0 |
| Meningioma benign | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Monoclonal gammopathy | 1 ( <0.1) | 6019.43 | 0.02 | 0 | 6141.44 | 0 |
| Myxoid liposarcoma | 1 ( <0.1) | 6018.46 | 0.02 | 0 | 6141.44 | 0 |
| Nasopharyngeal tumour | 1 ( <0.1) | 6019.49 | 0.02 | 0 | 6141.44 | 0 |
| Neoplasm malignant | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Paraneoplastic syndrome | 1 ( <0.1) | 6019.15 | 0.02 | 0 | 6141.44 | 0 |
| Small cell lung cancer | 1 ( <0.1) | 6018.89 | 0.02 | 1 ( <0.1) | 6141.37 | 0.02 |
| Tongue neoplasm | 1 ( <0.1) | 6019.74 | 0.02 | 0 | 6141.44 | 0 |
| Abdominal neoplasm | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.24 | 0.02 |
| Acute lymphocytic leukaemia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.40 | 0.02 |
| Adenocarcinoma metastatic | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.40 | 0.02 |
| Bladder neoplasm | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.05 | 0.02 |
| Colorectal adenoma | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.99 | 0.02 |
| Diffuse large B-cell lymphoma | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.52 | 0.02 |
| Intracranial tumour haemorrhage | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.42 | 0.02 |
| Laryngeal cancer | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.93 | 0.02 |
| Lung adenocarcinoma stage IV | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.30 | 0.02 |
| Metastatic bronchial carcinoma | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.42 | 0.02 |
| Myelodysplastic syndrome | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.65 | 0.02 |
| Nasal sinus cancer | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.61 | 0.02 |

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|---|---|---|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (cont.) | | | | | | |
| Non-Hodgkin's lymphoma | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.33 | 0.02 |
| Non-small cell lung cancer metastatic | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.39 | 0.02 |
| Pancreatic carcinoma metastatic | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.12 | 0.02 |
| Prostate cancer metastatic | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.28 | 0.02 |
| Renal cancer metastatic | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.02 | 0.02 |
| Small intestine carcinoma | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.11 | 0.02 |
| Squamous cell carcinoma of the parotid gland | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.34 | 0.02 |
| Ureteric cancer | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.23 | 0.02 |
| Vulval cancer | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.48 | 0.02 |

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|---|---|---|---|---|---|---|
| Gastrointestinal disorders | 33 ( 1.0) | 5993.15 | 0.55 | 29 ( 0.9) | 6119.48 | 0.47 |
| Dyspepsia | 5 ( 0.2) | 6016.72 | 0.08 | 1 ( <0.1) | 6139.23 | 0.02 |
| Nausea | 3 ( 0.1) | 6018.54 | 0.05 | 5 ( 0.2) | 6135.53 | 0.08 |
| Diarrhoea | 4 ( 0.1) | 6013.16 | 0.07 | 0 | 6141.44 | 0 |
| Gastrointestinal haemorrhage | 3 ( 0.1) | 6017.69 | 0.05 | 3 ( 0.1) | 6141.31 | 0.05 |
| Abdominal pain upper | 2 ( 0.1) | 6017.63 | 0.03 | 3 ( 0.1) | 6135.08 | 0.05 |
| Abdominal distension | 2 ( 0.1) | 6017.19 | 0.03 | 0 | 6141.44 | 0 |
| Constipation | 1 ( <0.1) | 6018.34 | 0.02 | 2 ( 0.1) | 6139.89 | 0.03 |
| Upper gastrointestinal haemorrhage | 0 | 6019.75 | 0 | 2 ( 0.1) | 6141.43 | 0.03 |
| Vomiting | 0 | 6019.75 | 0 | 2 ( 0.1) | 6138.54 | 0.03 |
| Abdominal pain | 1 ( <0.1) | 6018.60 | 0.02 | 0 | 6141.44 | 0 |
| Dry mouth | 1 ( <0.1) | 6019.03 | 0.02 | 0 | 6141.44 | 0 |
| Duodenal ulcer haemorrhage | 1 ( <0.1) | 6019.69 | 0.02 | 0 | 6141.44 | 0 |
| Flatulence | 1 ( <0.1) | 6018.05 | 0.02 | 0 | 6141.44 | 0 |
| Gastritis | 1 ( <0.1) | 6018.18 | 0.02 | 0 | 6141.44 | 0 |
| Gastrointestinal disorder | 1 ( <0.1) | 6017.24 | 0.02 | 0 | 6141.44 | 0 |
| Intestinal infarction | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Intestinal ischaemia | 1 ( <0.1) | 6019.74 | 0.02 | 1 ( <0.1) | 6141.39 | 0.02 |
| Intestinal perforation | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Obstructive pancreatitis | 1 ( <0.1) | 6019.70 | 0.02 | 0 | 6141.44 | 0 |
| Oesophageal haemorrhage | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Pancreatitis acute | 1 ( <0.1) | 6019.75 | 0.02 | 1 ( <0.1) | 6141.43 | 0.02 |
| Small intestinal haemorrhage | 1 ( <0.1) | 6019.49 | 0.02 | 0 | 6141.44 | 0 |
| Swollen tongue | 1 ( <0.1) | 6018.75 | 0.02 | 0 | 6141.44 | 0 |
| Colitis ischaemic | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.43 | 0.02 |
| Diverticular perforation | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.43 | 0.02 |
| Gastric ulcer | 0 | 6019.75 | 0 | 1 ( <0.1) | 6139.01 | 0.02 |
| Gastrointestinal perforation | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.24 | 0.02 |
| Ileus | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.34 | 0.02 |
| Intestinal obstruction | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.43 | 0.02 |
| Lower gastrointestinal haemorrhage | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.43 | 0.02 |
| Mesenteric artery thrombosis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.37 | 0.02 |
| Rectal haemorrhage | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.43 | 0.02 |

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|---|---|---|---|---|---|---|
| Vascular disorders | 30 ( 0.9) | 5992.87 | 0.50 | 26 ( 0.8) | 6120.77 | 0.42 |
| Hypotension | 11 ( 0.3) | 5999.61 | 0.18 | 13 ( 0.4) | 6129.25 | 0.21 |
| Peripheral arterial occlusive disease | 3 ( 0.1) | 6018.18 | 0.05 | 3 ( 0.1) | 6138.73 | 0.05 |
| Aortic aneurysm rupture | 2 ( 0.1) | 6019.58 | 0.03 | 0 | 6141.44 | 0 |
| Circulatory collapse | 2 ( 0.1) | 6019.75 | 0.03 | 0 | 6141.44 | 0 |
| Leriche syndrome | 0 | 6019.75 | 0 | 2 ( 0.1) | 6140.66 | 0.03 |
| Aortic aneurysm | 1 ( <0.1) | 6019.74 | 0.02 | 0 | 6141.44 | 0 |
| Aortic dissection | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Aortic stenosis | 1 ( <0.1) | 6019.29 | 0.02 | 1 ( <0.1) | 6141.31 | 0.02 |
| Extremity necrosis | 1 ( <0.1) | 6019.61 | 0.02 | 1 ( <0.1) | 6140.28 | 0.02 |
| Giant cell arteritis | 1 ( <0.1) | 6017.86 | 0.02 | 0 | 6141.44 | 0 |
| Haematoma | 1 ( <0.1) | 6019.66 | 0.02 | 0 | 6141.44 | 0 |
| Haemorrhagic infarction | 1 ( <0.1) | 6019.47 | 0.02 | 0 | 6141.44 | 0 |
| Hypertension | 1 ( <0.1) | 6019.66 | 0.02 | 0 | 6141.44 | 0 |
| Pallor | 1 ( <0.1) | 6017.76 | 0.02 | 0 | 6141.44 | 0 |
| Peripheral embolism | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Peripheral ischaemia | 1 ( <0.1) | 6019.70 | 0.02 | 1 ( <0.1) | 6141.27 | 0.02 |
| Shock haemorrhagic | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Dry gangrene | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.41 | 0.02 |
| Embolism | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.41 | 0.02 |
| Hot flush | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.15 | 0.02 |
| Thrombosis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6138.54 | 0.02 |
| Vasculitis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.12 | 0.02 |

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MedDRA version: 25.0

Table R.5.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Metabolism and nutrition disorders | 25 ( 0.8) | 6000.80 | 0.42 | 18 ( 0.5) | 6130.20 | 0.29 |
| Hypoglycaemia | 6 ( 0.2) | 6015.69 | 0.10 | 4 ( 0.1) | 6136.75 | 0.07 |
| Dehydration | 1 ( <0.1) | 6019.69 | 0.02 | 4 ( 0.1) | 6137.61 | 0.07 |
| Diabetes mellitus | 3 ( 0.1) | 6017.54 | 0.05 | 1 ( <0.1) | 6140.90 | 0.02 |
| Decreased appetite | 2 ( 0.1) | 6017.68 | 0.03 | 1 ( <0.1) | 6140.79 | 0.02 |
| Gout | 2 ( 0.1) | 6017.49 | 0.03 | 1 ( <0.1) | 6141.13 | 0.02 |
| Hyperkalaemia | 2 ( 0.1) | 6018.86 | 0.03 | 0 | 6141.44 | 0 |
| Metabolic acidosis | 1 ( <0.1) | 6019.17 | 0.02 | 2 ( 0.1) | 6141.32 | 0.03 |
| Adult failure to thrive | 1 ( <0.1) | 6019.52 | 0.02 | 0 | 6141.44 | 0 |
| Cachexia | 1 ( <0.1) | 6019.72 | 0.02 | 1 ( <0.1) | 6141.40 | 0.02 |
| Diabetes mellitus inadequate control | 1 ( <0.1) | 6018.18 | 0.02 | 0 | 6141.44 | 0 |
| Diabetic ketoacidosis | 1 ( <0.1) | 6018.35 | 0.02 | 0 | 6141.44 | 0 |
| Hyperglycaemic hyperosmolar nonketotic syndrome | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Hypovolaemia | 1 ( <0.1) | 6018.05 | 0.02 | 0 | 6141.44 | 0 |
| Ketoacidosis | 1 ( <0.1) | 6018.36 | 0.02 | 1 ( <0.1) | 6141.43 | 0.02 |
| Type 2 diabetes mellitus | 1 ( <0.1) | 6019.26 | 0.02 | 1 ( <0.1) | 6141.23 | 0.02 |
| Hypernatraemia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.28 | 0.02 |
| Hyponatraemia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.72 | 0.02 |

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MedDRA version: 25.0

Table R.5.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | 21 ( 0.6) | 6016.33 | 0.35 | 12 ( 0.4) | 6140.93 | 0.20 |
| Chronic obstructive pulmonary disease | 5 ( 0.2) | 6019.49 | 0.08 | 1 ( <0.1) | 6141.43 | 0.02 |
| Respiratory failure | 2 ( 0.1) | 6019.63 | 0.03 | 3 ( 0.1) | 6141.19 | 0.05 |
| Pulmonary embolism | 2 ( 0.1) | 6019.58 | 0.03 | 1 ( <0.1) | 6141.44 | 0.02 |
| Dyspnoea | 1 ( <0.1) | 6018.41 | 0.02 | 2 ( 0.1) | 6141.44 | 0.03 |
| Respiratory arrest | 0 | 6019.75 | 0 | 2 ( 0.1) | 6141.35 | 0.03 |
| Acute pulmonary oedema | 1 ( <0.1) | 6019.75 | 0.02 | 1 ( <0.1) | 6141.33 | 0.02 |
| Acute respiratory distress syndrome | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Acute respiratory failure | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Choking | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Cough | 1 ( <0.1) | 6019.68 | 0.02 | 0 | 6141.44 | 0 |
| Haemoptysis | 1 ( <0.1) | 6018.81 | 0.02 | 0 | 6141.44 | 0 |
| Idiopathic pulmonary fibrosis | 1 ( <0.1) | 6019.74 | 0.02 | 0 | 6141.44 | 0 |
| Pneumonitis | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Pulmonary arterial hypertension | 1 ( <0.1) | 6019.31 | 0.02 | 0 | 6141.44 | 0 |
| Pulmonary oedema | 1 ( <0.1) | 6019.75 | 0.02 | 0 | 6141.44 | 0 |
| Respiratory disorder | 1 ( <0.1) | 6019.69 | 0.02 | 0 | 6141.44 | 0 |
| Interstitial lung disease | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.42 | 0.02 |
| Pulmonary hypertension | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.39 | 0.02 |

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MedDRA version: 25.0

Table R.5.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Injury, poisoning and procedural complications | 11 ( 0.3) | 6015.51 | 0.18 | 19 ( 0.6) | 6136.58 | 0.31 |
| Fall | 3 ( 0.1) | 6019.54 | 0.05 | 3 ( 0.1) | 6140.93 | 0.05 |
| Upper limb fracture | 2 ( 0.1) | 6016.56 | 0.03 | 0 | 6141.44 | 0 |
| Hip fracture | 0 | 6019.75 | 0 | 2 ( 0.1) | 6141.25 | 0.03 |
| Subdural haematoma | 1 ( <0.1) | 6019.75 | 0.02 | 2 ( 0.1) | 6141.36 | 0.03 |
| Femoral neck fracture | 1 ( <0.1) | 6019.74 | 0.02 | 0 | 6141.44 | 0 |
| Multiple injuries | 1 ( <0.1) | 6019.72 | 0.02 | 0 | 6141.44 | 0 |
| Overdose | 1 ( <0.1) | 6019.26 | 0.02 | 0 | 6141.44 | 0 |
| Skin laceration | 1 ( <0.1) | 6019.47 | 0.02 | 0 | 6141.44 | 0 |
| Subdural haemorrhage | 1 ( <0.1) | 6019.74 | 0.02 | 0 | 6141.44 | 0 |
| Craniocerebral injury | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.43 | 0.02 |
| Femur fracture | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.32 | 0.02 |
| Fracture | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.44 | 0.02 |
| Limb traumatic amputation | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.22 | 0.02 |
| Perineal injury | 0 | 6019.75 | 0 | 1 ( <0.1) | 6139.84 | 0.02 |
| Procedural complication | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.41 | 0.02 |
| Road traffic accident | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.44 | 0.02 |
| Splenic rupture | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.44 | 0.02 |
| Traumatic fracture | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.85 | 0.02 |
| Traumatic intracranial haemorrhage | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.43 | 0.02 |
| Traumatic spinal cord compression | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.18 | 0.02 |
| Wrist fracture | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.17 | 0.02 |
| Investigations | 16 ( 0.5) | 6004.48 | 0.27 | 10 ( 0.3) | 6128.77 | 0.16 |
| Glomerular filtration rate decreased | 5 ( 0.2) | 6014.38 | 0.08 | 4 ( 0.1) | 6136.04 | 0.07 |
| Hepatic enzyme increased | 3 ( 0.1) | 6018.58 | 0.05 | 0 | 6141.44 | 0 |
| Blood bicarbonate decreased | 2 ( 0.1) | 6015.55 | 0.03 | 0 | 6141.44 | 0 |
| Blood creatinine increased | 2 ( 0.1) | 6018.86 | 0.03 | 2 ( 0.1) | 6137.94 | 0.03 |
| Alanine aminotransferase increased | 1 ( <0.1) | 6019.26 | 0.02 | 0 | 6141.44 | 0 |
| Aspartate aminotransferase increased | 1 ( <0.1) | 6019.26 | 0.02 | 1 ( <0.1) | 6141.41 | 0.02 |
| Gamma-glutamyltransferase increased | 1 ( <0.1) | 6019.44 | 0.02 | 0 | 6141.44 | 0 |
| Liver function test abnormal | 1 ( <0.1) | 6018.26 | 0.02 | 0 | 6141.44 | 0 |
| Urine ketone body present | 1 ( <0.1) | 6018.41 | 0.02 | 0 | 6141.44 | 0 |
| Blood creatine phosphokinase increased | 0 | 6019.75 | 0 | 1 ( <0.1) | 6139.93 | 0.02 |
| Neutrophil count decreased | 0 | 6019.75 | 0 | 1 ( <0.1) | 6139.46 | 0.02 |
| Weight decreased | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.17 | 0.02 |

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Table R.5.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | 12 ( 0.4) | 6004.60 | 0.20 | 16 ( 0.5) | 6121.77 | 0.26 |
| Pruritus | 3 ( 0.1) | 6014.72 | 0.05 | 4 ( 0.1) | 6135.31 | 0.07 |
| Rash | 1 ( <0.1) | 6019.63 | 0.02 | 3 ( 0.1) | 6136.95 | 0.05 |
| Diabetic foot | 1 ( <0.1) | 6018.54 | 0.02 | 2 ( 0.1) | 6141.10 | 0.03 |
| Skin ulcer | 1 ( <0.1) | 6019.15 | 0.02 | 2 ( 0.1) | 6138.60 | 0.03 |
| Ecchymosis | 1 ( <0.1) | 6018.98 | 0.02 | 0 | 6141.44 | 0 |
| Hyperhidrosis | 1 ( <0.1) | 6016.51 | 0.02 | 0 | 6141.44 | 0 |
| Pruritus allergic | 1 ( <0.1) | 6018.25 | 0.02 | 1 ( <0.1) | 6140.32 | 0.02 |
| Psoriasis | 1 ( <0.1) | 6019.47 | 0.02 | 0 | 6141.44 | 0 |
| Pyoderma gangrenosum | 1 ( <0.1) | 6019.50 | 0.02 | 0 | 6141.44 | 0 |
| Rash erythematous | 1 ( <0.1) | 6017.59 | 0.02 | 1 ( <0.1) | 6138.90 | 0.02 |
| Dermatitis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.14 | 0.02 |
| Eczema | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.90 | 0.02 |
| Granuloma annulare | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.05 | 0.02 |
| Musculoskeletal and connective tissue disorders | 8 ( 0.2) | 6013.00 | 0.13 | 4 ( 0.1) | 6138.25 | 0.07 |
| Pain in extremity | 3 ( 0.1) | 6015.89 | 0.05 | 1 ( <0.1) | 6140.26 | 0.02 |
| Flank pain | 1 ( <0.1) | 6019.68 | 0.02 | 0 | 6141.44 | 0 |
| Muscular weakness | 1 ( <0.1) | 6019.68 | 0.02 | 0 | 6141.44 | 0 |
| Myalgia | 1 ( <0.1) | 6017.83 | 0.02 | 0 | 6141.44 | 0 |
| Osteoarthritis | 1 ( <0.1) | 6019.10 | 0.02 | 0 | 6141.44 | 0 |
| Rheumatic disorder | 1 ( <0.1) | 6019.58 | 0.02 | 0 | 6141.44 | 0 |
| Back pain | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.83 | 0.02 |
| Polymyalgia rheumatica | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.05 | 0.02 |
| Sarcopenia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.42 | 0.02 |

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| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Psychiatric disorders | 7 ( 0.2) | 6012.83 | 0.12 | 7 ( 0.2) | 6132.26 | 0.11 |
| Insomnia | 2 ( 0.1) | 6016.62 | 0.03 | 0 | 6141.44 | 0 |
| Anxiety | 1 ( <0.1) | 6017.56 | 0.02 | 0 | 6141.44 | 0 |
| Completed suicide | 1 ( <0.1) | 6019.75 | 0.02 | 1 ( <0.1) | 6141.44 | 0.02 |
| Confusional state | 1 ( <0.1) | 6019.73 | 0.02 | 0 | 6141.44 | 0 |
| Mental status changes | 1 ( <0.1) | 6019.62 | 0.02 | 0 | 6141.44 | 0 |
| Nightmare | 1 ( <0.1) | 6018.30 | 0.02 | 0 | 6141.44 | 0 |
| Affect lability | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.13 | 0.02 |
| Alcoholism | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.91 | 0.02 |
| Depression | 0 | 6019.75 | 0 | 1 ( <0.1) | 6138.60 | 0.02 |
| Mood altered | 0 | 6019.75 | 0 | 1 ( <0.1) | 6139.57 | 0.02 |
| Paranoia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.37 | 0.02 |
| Poor quality sleep | 0 | 6019.75 | 0 | 1 ( <0.1) | 6139.88 | 0.02 |
| Hepatobiliary disorders | 5 ( 0.2) | 6015.43 | 0.08 | 7 ( 0.2) | 6136.05 | 0.11 |
| Liver injury | 1 ( <0.1) | 6018.33 | 0.02 | 2 ( 0.1) | 6139.45 | 0.03 |
| Cholangitis | 1 ( <0.1) | 6019.74 | 0.02 | 0 | 6141.44 | 0 |
| Cholestasis | 1 ( <0.1) | 6016.91 | 0.02 | 1 ( <0.1) | 6140.93 | 0.02 |
| Hepatic function abnormal | 1 ( <0.1) | 6019.73 | 0.02 | 1 ( <0.1) | 6141.11 | 0.02 |
| Hepatic mass | 1 ( <0.1) | 6019.72 | 0.02 | 0 | 6141.44 | 0 |
| Cholelithiasis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6139.50 | 0.02 |
| Hepatorenal syndrome | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.42 | 0.02 |
| Liver disorder | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.83 | 0.02 |
| Blood and lymphatic system disorders | 3 ( 0.1) | 6019.59 | 0.05 | 2 ( 0.1) | 6140.65 | 0.03 |
| Coagulopathy | 1 ( <0.1) | 6019.66 | 0.02 | 0 | 6141.44 | 0 |
| Disseminated intravascular coagulation | 1 ( <0.1) | 6019.73 | 0.02 | 0 | 6141.44 | 0 |
| Thrombocytopenia | 1 ( <0.1) | 6019.70 | 0.02 | 0 | 6141.44 | 0 |
| Blood loss anaemia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.14 | 0.02 |
| Pancytopenia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.94 | 0.02 |
| Ear and labyrinth disorders | 1 ( <0.1) | 6017.87 | 0.02 | 3 ( 0.1) | 6135.70 | 0.05 |
| Vertigo | 1 ( <0.1) | 6017.87 | 0.02 | 2 ( 0.1) | 6138.09 | 0.03 |
| Tinnitus | 0 | 6019.75 | 0 | 1 ( <0.1) | 6139.05 | 0.02 |
| Immune system disorders | 2 ( 0.1) | 6016.87 | 0.03 | 0 | 6141.44 | 0 |
| Corneal graft rejection | 1 ( <0.1) | 6019.47 | 0.02 | 0 | 6141.44 | 0 |
| Drug hypersensitivity | 1 ( <0.1) | 6017.15 | 0.02 | 0 | 6141.44 | 0 |

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Table R.5.2.2: 2 Frequency of patients with AEs leading to treatment discontinuation occurring up to the end of the study by SOC and PT - TS

| System organ class/ Preferred term | Placebo N (%) | Placebo Time at risk (pt-yrs) | Placebo Rate /100 pt-yrs | Empa 10mg N (%) | Empa 10mg Time at risk (pt-yrs) | Empa 10mg Rate /100 pt-yrs |
|---|---|---|---|---|---|---|
| Reproductive system and breast disorders | 2 ( 0.1) | 6018.06 | 0.03 | 2 ( 0.1) | 6140.35 | 0.03 |
| Benign prostatic hyperplasia | 1 ( <0.1) | 6018.94 | 0.02 | 0 | 6141.44 | 0 |
| Erectile dysfunction | 1 ( <0.1) | 6018.87 | 0.02 | 0 | 6141.44 | 0 |
| Prostatitis | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.89 | 0.02 |
| Vulvovaginal pruritus | 0 | 6019.75 | 0 | 1 ( <0.1) | 6140.90 | 0.02 |
| Endocrine disorders | 1 ( <0.1) | 6019.63 | 0.02 | 0 | 6141.44 | 0 |
| Hyperthyroidism | 1 ( <0.1) | 6019.63 | 0.02 | 0 | 6141.44 | 0 |
| Eye disorders | 1 ( <0.1) | 6017.88 | 0.02 | 0 | 6141.44 | 0 |
| Ocular hyperaemia | 1 ( <0.1) | 6017.88 | 0.02 | 0 | 6141.44 | 0 |
| Surgical and medical procedures | 1 ( <0.1) | 6019.56 | 0.02 | 1 ( <0.1) | 6141.44 | 0.02 |
| Hip arthroplasty | 1 ( <0.1) | 6019.56 | 0.02 | 0 | 6141.44 | 0 |
| Euthanasia | 0 | 6019.75 | 0 | 1 ( <0.1) | 6141.44 | 0.02 |

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MedDRA version: 25.0

**R.5.2.3**

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 31 | 0.9 | 3330 | 26 | 0.8 | 0.4665 | 0.83 | ( 0.49, 1.39) | 0.82 | (0.49, 1.39) | 0.00 | (-0.01, 0.00) | |
| Study | | | | | | | | | | | | | | 0.0988 |
| 1245.110 | 2001 | 22 | 1.1 | 2052 | 13 | 0.6 | 0.1090 | 0.58 | ( 0.29, 1.14) | 0.57 | (0.29, 1.14) | 0.00 | (-0.01, 0.00) | |
| 1245.121 | 1274 | 9 | 0.7 | 1278 | 13 | 1.0 | 0.3959 | 1.44 | ( 0.62, 3.36) | 1.44 | (0.62, 3.39) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.1252 |
| Male | 2023 | 22 | 1.1 | 2068 | 23 | 1.1 | 0.9418 | 1.02 | ( 0.57, 1.83) | 1.02 | (0.57, 1.84) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 9 | 0.7 | 1262 | 3 | 0.2 | 0.0836 | 0.34 | ( 0.09, 1.23) | 0.33 | (0.09, 1.23) | 0.00 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.2958 |
| <65 | 766 | 11 | 1.4 | 705 | 12 | 1.7 | 0.6957 | 1.18 | ( 0.52, 2.64) | 1.18 | (0.52, 2.69) | 0.00 | (-0.01, 0.02) | |
| >=65 | 2509 | 20 | 0.8 | 2625 | 14 | 0.5 | 0.2434 | 0.67 | ( 0.34, 1.32) | 0.67 | (0.34, 1.32) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.9813 |
| North America | 434 | 6 | 1.4 | 432 | 5 | 1.2 | 0.7645 | 0.84 | ( 0.26, 2.71) | 0.83 | (0.25, 2.75) | 0.00 | (-0.02, 0.01) | |
| Latin America | 931 | 8 | 0.9 | 944 | 8 | 0.8 | 0.9678 | 0.98 | ( 0.37, 2.62) | 0.98 | (0.37, 2.63) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 14 | 1.0 | 1361 | 12 | 0.9 | 0.6586 | 0.84 | ( 0.39, 1.81) | 0.84 | (0.39, 1.82) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 1 | 0.2 | 413 | 0 | 0 | 0.5461 | 0.49 | ( 0.05, 5.26) | 0.49 | (0.04, 5.34) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 2 | 1.2 | 180 | 1 | 0.6 | 0.6036 | 0.59 | ( 0.08, 4.48) | 0.58 | (0.08, 4.51) | -0.01 | (-0.03, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8030 |
| Diabetic | 1739 | 28 | 1.6 | 1779 | 24 | 1.3 | 0.5206 | 0.84 | ( 0.49, 1.44) | 0.84 | (0.48, 1.45) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 1536 | 3 | 0.2 | 1551 | 2 | 0.1 | 0.6470 | 0.66 | ( 0.11, 3.94) | 0.66 | (0.11, 3.95) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8261 |
| <30 | 1975 | 13 | 0.7 | 1930 | 11 | 0.6 | 0.7263 | 0.87 | ( 0.39, 1.92) | 0.87 | (0.39, 1.93) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1300 | 18 | 1.4 | 1400 | 15 | 1.1 | 0.4550 | 0.77 | ( 0.39, 1.52) | 0.77 | (0.39, 1.53) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9284 |
| <130 | 1684 | 13 | 0.8 | 1687 | 11 | 0.7 | 0.6787 | 0.85 | ( 0.38, 1.88) | 0.84 | (0.38, 1.89) | 0.00 | (-0.01, 0.00) | |
| >=130 | 1591 | 18 | 1.1 | 1643 | 15 | 0.9 | 0.5339 | 0.81 | ( 0.41, 1.59) | 0.80 | (0.40, 1.60) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8091 |
| <75 | 1653 | 16 | 1.0 | 1612 | 15 | 0.9 | 0.9032 | 0.96 | ( 0.48, 1.92) | 0.96 | (0.47, 1.94) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 10 | 1.0 | 1085 | 7 | 0.6 | 0.3754 | 0.65 | ( 0.25, 1.70) | 0.65 | (0.25, 1.71) | 0.00 | (-0.01, 0.00) | |
| >=85 | 617 | 5 | 0.8 | 633 | 4 | 0.6 | 0.6970 | 0.77 | ( 0.21, 2.85) | 0.77 | (0.21, 2.88) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5831 |
| <30 | 250 | 2 | 0.8 | 263 | 4 | 1.5 | 0.4556 | 1.79 | ( 0.38, 8.42) | 1.80 | (0.38, 8.63) | 0.01 | (-0.01, 0.03) | |
| 30 to <45 | 898 | 8 | 0.9 | 909 | 6 | 0.7 | 0.5810 | 0.74 | ( 0.26, 2.13) | 0.74 | (0.26, 2.15) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 21 | 1.0 | 2158 | 16 | 0.7 | 0.3829 | 0.75 | ( 0.39, 1.43) | 0.75 | (0.39, 1.44) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7565 |
| Normal (<30) | 1216 | 6 | 0.5 | 1243 | 7 | 0.6 | 0.8112 | 1.14 | ( 0.38, 3.39) | 1.14 | (0.38, 3.41) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 11 | 0.7 | 1546 | 9 | 0.6 | 0.6599 | 0.82 | ( 0.34, 1.97) | 0.82 | (0.34, 1.98) | 0.00 | (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 500 | 14 | 2.8 | 525 | 10 | 1.9 | 0.3484 | 0.68 | ( 0.30, 1.53) | 0.68 | (0.30, 1.54) | -0.01 | (-0.03, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7637 |
| Low, moderate or high | 2430 | 20 | 0.8 | 2495 | 18 | 0.7 | 0.6848 | 0.88 | ( 0.47, 1.65) | 0.88 | (0.46, 1.66) | 0.00 | (-0.01, 0.00) | |
| Very high | 834 | 11 | 1.3 | 820 | 8 | 1.0 | 0.5146 | 0.74 | ( 0.30, 1.83) | 0.74 | (0.30, 1.84) | 0.00 | (-0.01, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5751 |
| No | 572 | 4 | 0.7 | 578 | 2 | 0.3 | 0.4354 | 0.55 | ( 0.12, 2.54) | 0.55 | (0.12, 2.56) | 0.00 | (-0.01, 0.01) | |
| Yes | 2703 | 27 | 1.0 | 2752 | 24 | 0.9 | 0.6253 | 0.87 | ( 0.51, 1.51) | 0.87 | (0.50, 1.51) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2157 |
| No | 344 | 6 | 1.7 | 349 | 2 | 0.6 | 0.1456 | 0.32 | ( 0.06, 1.61) | 0.32 | (0.06, 1.60) | -0.01 | (-0.03, 0.00) | |
| Yes | 2931 | 25 | 0.9 | 2981 | 24 | 0.8 | 0.8391 | 0.94 | ( 0.54, 1.65) | 0.94 | (0.54, 1.65) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1327 |
| No | 275 | 4 | 1.5 | 307 | 0 | 0 | 0.0717 | 0.17 | ( 0.02, 1.50) | 0.17 | (0.02, 1.49) | -0.02 | (-0.03, 0.00) | |
| Yes | 3000 | 27 | 0.9 | 3023 | 26 | 0.9 | 0.8676 | 0.96 | ( 0.56, 1.63) | 0.96 | (0.56, 1.64) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 198 | 6.0 | 3330 | 161 | 4.8 | 0.0300 | 0.80 | ( 0.65, 0.98) | 0.79 | (0.64, 0.98) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.0692 |
| 1245.110 | 2001 | 129 | 6.4 | 2052 | 91 | 4.4 | 0.0047 | 0.69 | ( 0.53, 0.89) | 0.67 | (0.51, 0.89) | -0.02 | (-0.03,-0.01) | |
| 1245.121 | 1274 | 69 | 5.4 | 1278 | 70 | 5.5 | 0.9456 | 1.01 | ( 0.73, 1.40) | 1.01 | (0.72, 1.42) | 0.00 | (-0.02, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.1544 |
| Male | 2023 | 117 | 5.8 | 2068 | 107 | 5.2 | 0.3929 | 0.89 | ( 0.69, 1.15) | 0.89 | (0.68, 1.16) | -0.01 | (-0.02, 0.01) | |
| Female | 1252 | 81 | 6.5 | 1262 | 54 | 4.3 | 0.0140 | 0.66 | ( 0.47, 0.92) | 0.64 | (0.45, 0.92) | -0.02 | (-0.04, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.0693 |
| <65 | 766 | 50 | 6.5 | 705 | 50 | 7.1 | 0.6697 | 1.09 | ( 0.74, 1.59) | 1.09 | (0.73, 1.64) | 0.01 | (-0.02, 0.03) | |
| >=65 | 2509 | 148 | 5.9 | 2625 | 111 | 4.2 | 0.0063 | 0.72 | ( 0.56, 0.91) | 0.70 | (0.55, 0.91) | -0.02 | (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | | 0.4959 |
| North America | 434 | 30 | 6.9 | 432 | 21 | 4.9 | 0.1997 | 0.70 | ( 0.41, 1.21) | 0.69 | (0.39, 1.22) | -0.02 | (-0.05, 0.01) | |
| Latin America | 931 | 46 | 4.9 | 944 | 47 | 5.0 | 0.9631 | 1.01 | ( 0.68, 1.50) | 1.01 | (0.67, 1.53) | 0.00 | (-0.02, 0.02) | |
| Europe | 1334 | 65 | 4.9 | 1361 | 42 | 3.1 | 0.0176 | 0.63 | ( 0.43, 0.93) | 0.62 | (0.42, 0.92) | -0.02 | (-0.03, 0.00) | |
| Asia | 405 | 49 | 12.1 | 413 | 42 | 10.2 | 0.4004 | 0.85 | ( 0.58, 1.25) | 0.83 | (0.54, 1.28) | -0.02 | (-0.06, 0.02) | |
| Other | 171 | 8 | 4.7 | 180 | 9 | 5.0 | 0.9299 | 1.04 | ( 0.41, 2.63) | 1.05 | (0.39, 2.78) | 0.00 | (-0.04, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6379 |
| Diabetic | 1739 | 109 | 6.3 | 1779 | 93 | 5.2 | 0.1860 | 0.83 | ( 0.64, 1.09) | 0.83 | (0.62, 1.10) | -0.01 | (-0.03, 0.01) | |
| Non-Diabetic | 1536 | 89 | 5.8 | 1551 | 68 | 4.4 | 0.0744 | 0.76 | ( 0.56, 1.03) | 0.75 | (0.54, 1.03) | -0.01 | (-0.03, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3119 |
| <30 | 1975 | 145 | 7.3 | 1930 | 107 | 5.5 | 0.0222 | 0.76 | ( 0.59, 0.96) | 0.74 | (0.57, 0.96) | -0.02 | (-0.03, 0.00) | |
| >=30 | 1300 | 53 | 4.1 | 1400 | 54 | 3.9 | 0.7865 | 0.95 | ( 0.65, 1.38) | 0.95 | (0.64, 1.40) | 0.00 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4320 |
| <130 | 1684 | 114 | 6.8 | 1687 | 98 | 5.8 | 0.2471 | 0.86 | ( 0.66, 1.11) | 0.85 | (0.64, 1.12) | -0.01 | (-0.03, 0.01) | |
| >=130 | 1591 | 84 | 5.3 | 1643 | 63 | 3.8 | 0.0490 | 0.73 | ( 0.53,>1.00) | 0.72 | (0.51, 1.00) | -0.01 | (-0.03, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2609 |
| <75 | 1653 | 105 | 6.4 | 1612 | 89 | 5.5 | 0.3154 | 0.87 | ( 0.66, 1.14) | 0.86 | (0.64, 1.15) | -0.01 | (-0.02, 0.01) | |
| 75 to <85 | 1005 | 58 | 5.8 | 1085 | 38 | 3.5 | 0.0135 | 0.61 | ( 0.41, 0.91) | 0.59 | (0.39, 0.90) | -0.02 | (-0.04, 0.00) | |
| >=85 | 617 | 35 | 5.7 | 633 | 34 | 5.4 | 0.8134 | 0.95 | ( 0.60, 1.50) | 0.94 | (0.58, 1.53) | 0.00 | (-0.03, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9973 |
| <30 | 250 | 22 | 8.8 | 263 | 19 | 7.2 | 0.4977 | 0.81 | ( 0.45, 1.47) | 0.80 | (0.42, 1.52) | -0.02 | (-0.06, 0.03) | |
| 30 to <45 | 898 | 46 | 5.1 | 909 | 37 | 4.1 | 0.2832 | 0.79 | ( 0.52, 1.21) | 0.79 | (0.51, 1.22) | -0.01 | (-0.03, 0.01) | |
| >=45 | 2126 | 130 | 6.1 | 2158 | 105 | 4.9 | 0.0734 | 0.80 | ( 0.62, 1.02) | 0.79 | (0.60, 1.02) | -0.01 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3947 |
| Normal (<30) | 1216 | 64 | 5.3 | 1243 | 43 | 3.5 | 0.0279 | 0.66 | ( 0.45, 0.96) | 0.64 | (0.43, 0.96) | -0.02 | (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 101 | 6.5 | 1546 | 85 | 5.5 | 0.2304 | 0.84 | ( 0.64, 1.11) | 0.83 | (0.62, 1.12) | -0.01 | (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 500 | 32 | 6.4 | 525 | 33 | 6.3 | 0.9196 | 0.98 | ( 0.61, 1.57) | 0.97 | (0.59, 1.61) | 0.00 | (-0.03, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2247 |
| Low, moderate or high | 2430 | 143 | 5.9 | 2495 | 109 | 4.4 | 0.0155 | 0.74 | ( 0.58, 0.95) | 0.73 | (0.57, 0.94) | -0.02 | (-0.03, 0.00) | |
| Very high | 834 | 54 | 6.5 | 820 | 52 | 6.3 | 0.8963 | 0.98 | ( 0.67, 1.41) | 0.97 | (0.66, 1.44) | 0.00 | (-0.03, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.8212 |
| No | 572 | 45 | 7.9 | 578 | 38 | 6.6 | 0.3941 | 0.83 | ( 0.55, 1.27) | 0.82 | (0.53, 1.29) | -0.01 | (-0.04, 0.02) | |
| Yes | 2703 | 153 | 5.7 | 2752 | 123 | 4.5 | 0.0449 | 0.79 | ( 0.63,<1.00) | 0.78 | (0.61, 0.99) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7077 |
| No | 344 | 28 | 8.1 | 349 | 21 | 6.0 | 0.2457 | 0.72 | ( 0.42, 1.26) | 0.71 | (0.39, 1.27) | -0.02 | (-0.06, 0.02) | |
| Yes | 2931 | 170 | 5.8 | 2981 | 140 | 4.7 | 0.0566 | 0.81 | ( 0.65, 1.01) | 0.80 | (0.64, 1.01) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.0151 |
| No | 275 | 15 | 5.5 | 307 | 3 | 1.0 | 0.0023 | 0.20 ( 0.06, 0.64) | 0.19 (0.06, 0.62) | -0.04 (-0.07,-0.02) | |
| Yes | 3000 | 183 | 6.1 | 3023 | 158 | 5.2 | 0.1421 | 0.86 ( 0.70, 1.05) | 0.85 (0.68, 1.06) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 6 | 0.2 | 3330 | 6 | 0.2 | 0.9686 | 0.98 | ( 0.33, 2.90) | 0.98 | (0.33, 2.91) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.4696 |
| 1245.110 | 2001 | 5 | 0.2 | 2052 | 6 | 0.3 | 0.7948 | 1.17 | ( 0.36, 3.83) | 1.17 | (0.36, 3.84) | 0.00 | ( 0.00, 0.00) | |
| 1245.121 | 1274 | 1 | 0.1 | 1278 | 0 | 0 | 0.4780 | 0.33 | ( 0.01, 8.15) | 0.33 | (0.01, 8.16) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | |
| Male | 2023 | 3 | 0.1 | 2068 | 3 | 0.1 | | | | | | | | |
| Female | 1252 | 3 | 0.2 | 1262 | 3 | 0.2 | | | | | | | | |
| Age [years] | | | | | | | | | | | | | | |
| <65 | 766 | 6 | 0.8 | 705 | 1 | 0.1 | | | | | | | | |
| >=65 | 2509 | 0 | 0 | 2625 | 5 | 0.2 | | | | | | | | |
| Region | | | | | | | | | | | | | | |
| North America | 434 | 2 | 0.5 | 432 | 3 | 0.7 | | | | | | | | |
| Latin America | 931 | 1 | 0.1 | 944 | 0 | 0 | | | | | | | | |
| Europe | 1334 | 0 | 0 | 1361 | 1 | 0.1 | | | | | | | | |
| Asia | 405 | 1 | 0.2 | 413 | 0 | 0 | | | | | | | | |
| Other | 171 | 2 | 1.2 | 180 | 2 | 1.1 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9885 |
| Diabetic | 1739 | 6 | 0.3 | 1779 | 6 | 0.3 | 0.9574 | 0.97 | ( 0.33, 2.88) | 0.97 | (0.33, 2.89) | 0.00 | ( 0.00, 0.00) | |
| Non-Diabetic | 1536 | 0 | 0 | 1551 | 0 | 0 | 0.9956 | 0.99 | ( 0.06,15.85) | 0.99 | (0.06,15.88) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | |
| <30 | 1975 | 3 | 0.2 | 1930 | 2 | 0.1 | | | | | | | | |
| >=30 | 1300 | 3 | 0.2 | 1400 | 4 | 0.3 | | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | |
| <130 | 1684 | 2 | 0.1 | 1687 | 1 | 0.1 | | | | | | | | |
| >=130 | 1591 | 4 | 0.3 | 1643 | 5 | 0.3 | | | | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 1653 | 1 | 0.1 | 1612 | 3 | 0.2 | | | | | |
| 75 to <85 | 1005 | 3 | 0.3 | 1085 | 3 | 0.3 | | | | | |
| >=85 | 617 | 2 | 0.3 | 633 | 0 | 0 | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 250 | 2 | 0.8 | 263 | 1 | 0.4 | | | | | |
| 30 to <45 | 898 | 1 | 0.1 | 909 | 2 | 0.2 | | | | | |
| >=45 | 2126 | 3 | 0.1 | 2158 | 3 | 0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 1216 | 1 | 0.1 | 1243 | 1 | 0.1 | | | | | |
| Microalbuminuria (30 to <=300) | 1548 | 3 | 0.2 | 1546 | 2 | 0.1 | | | | | |
| Macroalbuminuria (>300) | 500 | 2 | 0.4 | 525 | 3 | 0.6 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 2430 | 4 | 0.2 | 2495 | 4 | 0.2 | | | | | |
| Very high | 834 | 2 | 0.2 | 820 | 2 | 0.2 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 572 | 2 | 0.3 | 578 | 1 | 0.2 | | | | | |
| Yes | 2703 | 4 | 0.1 | 2752 | 5 | 0.2 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.2596 |
| No | 344 | 0 | 0 | 349 | 2 | 0.6 | 0.3278 | 2.89 ( 0.31,26.81) | 2.91 (0.31,27.66) | 0.01 (-0.01, 0.02) | |
| Yes | 2931 | 6 | 0.2 | 2981 | 4 | 0.1 | 0.5185 | 0.67 ( 0.20, 2.24) | 0.67 (0.20, 2.25) | 0.00 ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 275 | 1 | 0.4 | 307 | 2 | 0.7 | | | | | |
| Yes | 3000 | 5 | 0.2 | 3023 | 4 | 0.1 | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
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Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 117 | 3.6 | 3330 | 116 | 3.5 | 0.8300 | 0.97 | ( 0.76, 1.25) | 0.97 | (0.75, 1.26) | 0.00 | (-0.01, 0.01) | |
| Study | | | | | | | | | | | | | | 0.9758 |
| 1245.110 | 2001 | 84 | 4.2 | 2052 | 84 | 4.1 | 0.8677 | 0.98 | ( 0.73, 1.31) | 0.97 | (0.72, 1.33) | 0.00 | (-0.01, 0.01) | |
| 1245.121 | 1274 | 33 | 2.6 | 1278 | 32 | 2.5 | 0.8899 | 0.97 | ( 0.60, 1.56) | 0.97 | (0.59, 1.58) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.9581 |
| Male | 2023 | 71 | 3.5 | 2068 | 71 | 3.4 | 0.8895 | 0.98 | ( 0.71, 1.35) | 0.98 | (0.70, 1.37) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 46 | 3.7 | 1262 | 45 | 3.6 | 0.8580 | 0.96 | ( 0.64, 1.44) | 0.96 | (0.63, 1.46) | 0.00 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.8858 |
| <65 | 766 | 31 | 4.0 | 705 | 29 | 4.1 | 0.9682 | 1.01 | ( 0.62, 1.66) | 1.01 | (0.60, 1.70) | 0.00 | (-0.02, 0.02) | |
| >=65 | 2509 | 86 | 3.4 | 2625 | 87 | 3.3 | 0.8299 | 0.97 | ( 0.72, 1.30) | 0.97 | (0.71, 1.31) | 0.00 | (-0.01, 0.01) | |
| Region | | | | | | | | | | | | | | 0.6015 |
| North America | 434 | 19 | 4.4 | 432 | 28 | 6.5 | 0.1731 | 1.48 | ( 0.84, 2.61) | 1.51 | (0.83, 2.75) | 0.02 | (-0.01, 0.05) | |
| Latin America | 931 | 42 | 4.5 | 944 | 37 | 3.9 | 0.5553 | 0.88 | ( 0.57, 1.35) | 0.87 | (0.55, 1.37) | -0.01 | (-0.02, 0.01) | |
| Europe | 1334 | 34 | 2.5 | 1361 | 32 | 2.4 | 0.7262 | 0.92 | ( 0.57, 1.48) | 0.92 | (0.56, 1.49) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 13 | 3.2 | 413 | 10 | 2.4 | 0.4994 | 0.75 | ( 0.33, 1.71) | 0.75 | (0.32, 1.73) | -0.01 | (-0.03, 0.01) | |
| Other | 171 | 9 | 5.3 | 180 | 9 | 5.0 | 0.8966 | 0.94 | ( 0.38, 2.31) | 0.94 | (0.36, 2.43) | 0.00 | (-0.05, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3390 |
| Diabetic | 1739 | 108 | 6.2 | 1779 | 103 | 5.8 | 0.5796 | 0.93 | ( 0.72, 1.21) | 0.92 | (0.70, 1.22) | 0.00 | (-0.02, 0.01) | |
| Non-Diabetic | 1536 | 9 | 0.6 | 1551 | 13 | 0.8 | 0.4043 | 1.43 | ( 0.61, 3.34) | 1.43 | (0.61, 3.36) | 0.00 | ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3442 |
| <30 | 1975 | 64 | 3.2 | 1930 | 54 | 2.8 | 0.3895 | 0.86 | ( 0.60, 1.22) | 0.85 | (0.59, 1.23) | 0.00 | (-0.02, 0.01) | |
| >=30 | 1300 | 53 | 4.1 | 1400 | 62 | 4.4 | 0.6316 | 1.09 | ( 0.76, 1.56) | 1.10 | (0.75, 1.59) | 0.00 | (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7874 |
| <130 | 1684 | 50 | 3.0 | 1687 | 47 | 2.8 | 0.7240 | 0.93 | ( 0.63, 1.38) | 0.93 | (0.62, 1.39) | 0.00 | (-0.01, 0.01) | |
| >=130 | 1591 | 67 | 4.2 | 1643 | 69 | 4.2 | 0.9989 | 1.00 | ( 0.72, 1.39) | 1.00 | (0.71, 1.41) | 0.00 | (-0.01, 0.01) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5257 |
| <75 | 1653 | 66 | 4.0 | 1612 | 55 | 3.4 | 0.3501 | 0.85 | ( 0.60, 1.20) | 0.84 | (0.58, 1.21) | -0.01 | (-0.02, 0.01) | |
| 75 to <85 | 1005 | 29 | 2.9 | 1085 | 35 | 3.2 | 0.6469 | 1.12 | ( 0.69, 1.82) | 1.12 | (0.68, 1.85) | 0.00 | (-0.01, 0.02) | |
| >=85 | 617 | 22 | 3.6 | 633 | 26 | 4.1 | 0.6179 | 1.15 | ( 0.66, 2.01) | 1.16 | (0.65, 2.07) | 0.01 | (-0.02, 0.03) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3002 |
| <30 | 250 | 18 | 7.2 | 263 | 26 | 9.9 | 0.1858 | 1.47 | ( 0.83, 2.61) | 1.53 | (0.81, 2.89) | 0.03 | (-0.02, 0.08) | |
| 30 to <45 | 898 | 37 | 4.1 | 909 | 32 | 3.5 | 0.4958 | 0.85 | ( 0.54, 1.35) | 0.85 | (0.52, 1.37) | -0.01 | (-0.02, 0.01) | |
| >=45 | 2126 | 62 | 2.9 | 2158 | 58 | 2.7 | 0.6310 | 0.92 | ( 0.64, 1.31) | 0.91 | (0.64, 1.32) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6136 |
| Normal (<30) | 1216 | 27 | 2.2 | 1243 | 27 | 2.2 | 0.9305 | 0.98 | ( 0.58, 1.65) | 0.98 | (0.57, 1.67) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 48 | 3.1 | 1546 | 53 | 3.4 | 0.6296 | 1.10 | ( 0.75, 1.61) | 1.10 | (0.74, 1.64) | 0.00 | (-0.01, 0.02) | |
| Macroalbuminuria (>300) | 500 | 42 | 8.4 | 525 | 36 | 6.9 | 0.3705 | 0.82 | ( 0.54, 1.26) | 0.81 | (0.51, 1.29) | -0.01 | (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4829 |
| Low, moderate or high | 2430 | 63 | 2.6 | 2495 | 59 | 2.4 | 0.5984 | 0.91 | ( 0.64, 1.29) | 0.91 | (0.63, 1.30) | 0.00 | (-0.01, 0.01) | |
| Very high | 834 | 54 | 6.5 | 820 | 57 | 7.0 | 0.6410 | 1.09 | ( 0.76, 1.56) | 1.10 | (0.74, 1.62) | 0.01 | (-0.02, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9225 |
| No | 572 | 23 | 4.0 | 578 | 22 | 3.8 | 0.8535 | 0.95 | ( 0.53, 1.68) | 0.95 | (0.52, 1.72) | 0.00 | (-0.02, 0.02) | |
| Yes | 2703 | 94 | 3.5 | 2752 | 94 | 3.4 | 0.8760 | 0.98 | ( 0.74, 1.29) | 0.98 | (0.73, 1.31) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6300 |
| No | 344 | 12 | 3.5 | 349 | 10 | 2.9 | 0.5915 | 0.80 | ( 0.35, 1.81) | 0.79 | (0.34, 1.86) | -0.01 | (-0.03, 0.02) | |
| Yes | 2931 | 105 | 3.6 | 2981 | 106 | 3.6 | 0.9258 | 0.99 | ( 0.76, 1.29) | 0.99 | (0.75, 1.30) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2717 |
| No | 275 | 13 | 4.7 | 307 | 9 | 2.9 | 0.2626 | 0.62 | ( 0.27, 1.44) | 0.61 | (0.26, 1.45) | -0.02 | (-0.05, 0.01) | |
| Yes | 3000 | 104 | 3.5 | 3023 | 107 | 3.5 | 0.8925 | 1.02 | ( 0.78, 1.33) | 1.02 | (0.77, 1.34) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 284 | 8.7 | 3330 | 341 | 10.2 | 0.0317 | 1.18 | ( 1.01, 1.37) | 1.20 | (1.02, 1.42) | 0.02 | ( 0.00, 0.03) | |
| Study | | | | | | | | | | | | | | 0.4769 |
| 1245.110 | 2001 | 206 | 10.3 | 2052 | 257 | 12.5 | 0.0257 | 1.22 | ( 1.02, 1.45) | 1.25 | (1.03, 1.52) | 0.02 | ( 0.00, 0.04) | |
| 1245.121 | 1274 | 78 | 6.1 | 1278 | 84 | 6.6 | 0.6409 | 1.07 | ( 0.80, 1.45) | 1.08 | (0.78, 1.48) | 0.00 | (-0.01, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.0832 |
| Male | 2023 | 120 | 5.9 | 2068 | 123 | 5.9 | 0.9884 | 1.00 | ( 0.79, 1.28) | 1.00 | (0.77, 1.30) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 164 | 13.1 | 1262 | 218 | 17.3 | 0.0040 | 1.31 | ( 1.09, 1.58) | 1.38 | (1.11, 1.72) | 0.04 | ( 0.01, 0.07) | |
| Age [years] | | | | | | | | | | | | | | 0.7500 |
| <65 | 766 | 48 | 6.3 | 705 | 55 | 7.8 | 0.2589 | 1.24 | ( 0.85, 1.80) | 1.26 | (0.84, 1.88) | 0.02 | (-0.01, 0.04) | |
| >=65 | 2509 | 236 | 9.4 | 2625 | 286 | 10.9 | 0.0734 | 1.16 | ( 0.99, 1.37) | 1.18 | (0.98, 1.42) | 0.02 | ( 0.00, 0.03) | |
| Region | | | | | | | | | | | | | | 0.2548 |
| North America | 434 | 61 | 14.1 | 432 | 56 | 13.0 | 0.6313 | 0.92 | ( 0.66, 1.29) | 0.91 | (0.61, 1.34) | -0.01 | (-0.06, 0.03) | |
| Latin America | 931 | 70 | 7.5 | 944 | 95 | 10.1 | 0.0424 | 1.35 | ( 1.01, 1.81) | 1.40 | (1.01, 1.93) | 0.03 | ( 0.00, 0.05) | |
| Europe | 1334 | 118 | 8.8 | 1361 | 134 | 9.8 | 0.3839 | 1.11 | ( 0.88, 1.40) | 1.12 | (0.87, 1.46) | 0.01 | (-0.01, 0.03) | |
| Asia | 405 | 17 | 4.2 | 413 | 22 | 5.3 | 0.4801 | 1.25 | ( 0.68, 2.30) | 1.26 | (0.66, 2.41) | 0.01 | (-0.02, 0.04) | |
| Other | 171 | 18 | 10.5 | 180 | 34 | 18.9 | 0.0339 | 1.75 | ( 1.03, 2.97) | 1.95 | (1.05, 3.62) | 0.08 | ( 0.01, 0.15) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3742 |
| Diabetic | 1739 | 161 | 9.3 | 1779 | 183 | 10.3 | 0.3181 | 1.11 | ( 0.91, 1.35) | 1.12 | (0.90, 1.40) | 0.01 | (-0.01, 0.03) | |
| Non-Diabetic | 1536 | 123 | 8.0 | 1551 | 158 | 10.2 | 0.0363 | 1.27 | ( 1.01, 1.59) | 1.30 | (1.02, 1.67) | 0.02 | ( 0.00, 0.04) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4064 |
| <30 | 1975 | 157 | 7.9 | 1930 | 171 | 8.9 | 0.3520 | 1.10 | ( 0.90, 1.36) | 1.11 | (0.89, 1.40) | 0.01 | (-0.01, 0.03) | |
| >=30 | 1300 | 127 | 9.8 | 1400 | 170 | 12.1 | 0.0413 | 1.25 | ( 1.01, 1.55) | 1.29 | (1.01, 1.64) | 0.02 | ( 0.00, 0.05) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4584 |
| <130 | 1684 | 134 | 8.0 | 1687 | 169 | 10.0 | 0.0433 | 1.25 | ( 1.01, 1.55) | 1.28 | (1.01, 1.62) | 0.02 | ( 0.00, 0.04) | |
| >=130 | 1591 | 150 | 9.4 | 1643 | 172 | 10.5 | 0.3039 | 1.11 | ( 0.91, 1.37) | 1.13 | (0.90, 1.42) | 0.01 | (-0.01, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9707 |
| <75 | 1653 | 155 | 9.4 | 1612 | 177 | 11.0 | 0.1491 | 1.16 | ( 0.95, 1.42) | 1.18 | (0.94, 1.49) | 0.02 | (-0.01, 0.04) | |
| 75 to <85 | 1005 | 84 | 8.4 | 1085 | 108 | 10.0 | 0.2010 | 1.19 | ( 0.91, 1.57) | 1.22 | (0.90, 1.64) | 0.02 | (-0.01, 0.04) | |
| >=85 | 617 | 45 | 7.3 | 633 | 56 | 8.8 | 0.2984 | 1.22 | ( 0.84, 1.77) | 1.24 | (0.82, 1.87) | 0.02 | (-0.01, 0.05) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0369 |
| <30 | 250 | 32 | 12.8 | 263 | 38 | 14.4 | 0.4587 | 1.18 | ( 0.76, 1.85) | 1.22 | (0.73, 2.03) | 0.02 | (-0.04, 0.08) | |
| 30 to <45 | 898 | 108 | 12.0 | 909 | 99 | 10.9 | 0.4272 | 0.90 | ( 0.70, 1.16) | 0.89 | (0.66, 1.19) | -0.01 | (-0.04, 0.02) | |
| >=45 | 2126 | 144 | 6.8 | 2158 | 204 | 9.5 | 0.0017 | 1.38 | ( 1.13, 1.70) | 1.43 | (1.14, 1.78) | 0.03 | ( 0.01, 0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6613 |
| Normal (<30) | 1216 | 102 | 8.4 | 1243 | 127 | 10.2 | 0.1229 | 1.21 | ( 0.95, 1.55) | 1.24 | (0.94, 1.63) | 0.02 | ( 0.00, 0.04) | |
| Microalbuminuria (30 to <=300) | 1548 | 143 | 9.2 | 1546 | 161 | 10.4 | 0.2933 | 1.12 | ( 0.91, 1.39) | 1.14 | (0.90, 1.44) | 0.01 | (-0.01, 0.03) | |
| Macroalbuminuria (>300) | 500 | 37 | 7.4 | 525 | 53 | 10.1 | 0.1169 | 1.38 | ( 0.92, 2.05) | 1.42 | (0.91, 2.21) | 0.03 | (-0.01, 0.06) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1283 |
| Low, moderate or high | 2430 | 183 | 7.5 | 2495 | 244 | 9.8 | 0.0061 | 1.29 | ( 1.07, 1.55) | 1.32 | (1.08, 1.62) | 0.02 | ( 0.01, 0.04) | |
| Very high | 834 | 99 | 11.9 | 820 | 97 | 11.8 | 0.9565 | 1.01 | ( 0.78, 1.31) | 1.01 | (0.75, 1.36) | 0.00 | (-0.03, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2409 |
| No | 572 | 57 | 10.0 | 578 | 80 | 13.8 | 0.0394 | 1.40 | ( 1.01, 1.92) | 1.46 | (1.02, 2.10) | 0.04 | ( 0.00, 0.08) | |
| Yes | 2703 | 227 | 8.4 | 2752 | 261 | 9.5 | 0.1746 | 1.12 | ( 0.95, 1.33) | 1.14 | (0.94, 1.37) | 0.01 | ( 0.00, 0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9330 |
| No | 344 | 35 | 10.2 | 349 | 41 | 11.7 | 0.5033 | 1.16 | ( 0.76, 1.77) | 1.18 | (0.73, 1.89) | 0.02 | (-0.03, 0.06) | |
| Yes | 2931 | 249 | 8.5 | 2981 | 300 | 10.1 | 0.0432 | 1.18 | (>1.00, 1.38) | 1.20 | (1.01, 1.43) | 0.02 | ( 0.00, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.2392 |
| No | 275 | 22 | 8.0 | 307 | 38 | 12.4 | 0.0741 | 1.57 ( 0.95, 2.57) | 1.65 (0.95, 2.87) | 0.05 ( 0.00, 0.09) | |
| Yes | 3000 | 262 | 8.7 | 3023 | 303 | 10.0 | 0.0918 | 1.14 ( 0.98, 1.34) | 1.16 (0.98, 1.38) | 0.01 ( 0.00, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 28 | 0.9 | 3330 | 68 | 2.0 | <0.0001 | 2.38 | ( 1.54, 3.69) | 2.41 | (1.55, 3.76) | 0.01 | ( 0.01, 0.02) | |
| Study | | | | | | | | | | | | | | 0.8986 |
| 1245.110 | 2001 | 20 | 1.0 | 2052 | 48 | 2.3 | 0.0009 | 2.34 | ( 1.39, 3.93) | 2.37 | (1.40, 4.01) | 0.01 | ( 0.01, 0.02) | |
| 1245.121 | 1274 | 8 | 0.6 | 1278 | 20 | 1.6 | 0.0231 | 2.49 | ( 1.10, 5.64) | 2.52 | (1.10, 5.73) | 0.01 | ( 0.00, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.8662 |
| Male | 2023 | 15 | 0.7 | 2068 | 38 | 1.8 | 0.0020 | 2.47 | ( 1.37, 4.48) | 2.51 | (1.37, 4.57) | 0.01 | ( 0.00, 0.02) | |
| Female | 1252 | 13 | 1.0 | 1262 | 30 | 2.4 | 0.0093 | 2.29 | ( 1.20, 4.37) | 2.33 | (1.21, 4.48) | 0.01 | ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.1948 |
| <65 | 766 | 10 | 1.3 | 705 | 14 | 2.0 | 0.3049 | 1.52 | ( 0.68, 3.40) | 1.53 | (0.68, 3.46) | 0.01 | (-0.01, 0.02) | |
| >=65 | 2509 | 18 | 0.7 | 2625 | 54 | 2.1 | <0.0001 | 2.87 | ( 1.69, 4.88) | 2.92 | (1.71, 4.99) | 0.01 | ( 0.01, 0.02) | |
| Region | | | | | | | | | | | | | | 0.4423 |
| North America | 434 | 9 | 2.1 | 432 | 20 | 4.6 | 0.0370 | 2.23 | ( 1.03, 4.83) | 2.29 | (1.03, 5.10) | 0.03 | ( 0.00, 0.05) | |
| Latin America | 931 | 6 | 0.6 | 944 | 16 | 1.7 | 0.0342 | 2.64 | ( 1.04, 6.73) | 2.67 | (1.04, 6.86) | 0.01 | ( 0.00, 0.02) | |
| Europe | 1334 | 8 | 0.6 | 1361 | 27 | 2.0 | 0.0015 | 3.31 | ( 1.51, 7.28) | 3.36 | (1.52, 7.42) | 0.01 | ( 0.01, 0.02) | |
| Asia | 405 | 2 | 0.5 | 413 | 1 | 0.2 | 0.6368 | 0.66 | ( 0.11, 3.80) | 0.66 | (0.11, 3.88) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 3 | 1.8 | 180 | 4 | 2.2 | 0.8024 | 1.19 | ( 0.30, 4.74) | 1.20 | (0.29, 4.94) | 0.00 | (-0.03, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4206 |
| Diabetic | 1739 | 20 | 1.2 | 1779 | 43 | 2.4 | 0.0048 | 2.09 | ( 1.24, 3.54) | 2.12 | (1.24, 3.62) | 0.01 | ( 0.00, 0.02) | |
| Non-Diabetic | 1536 | 8 | 0.5 | 1551 | 25 | 1.6 | 0.0032 | 3.10 | ( 1.40, 6.85) | 3.13 | (1.41, 6.96) | 0.01 | ( 0.00, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9840 |
| <30 | 1975 | 13 | 0.7 | 1930 | 30 | 1.6 | 0.0075 | 2.36 | ( 1.23, 4.51) | 2.38 | (1.24, 4.58) | 0.01 | ( 0.00, 0.02) | |
| >=30 | 1300 | 15 | 1.2 | 1400 | 38 | 2.7 | 0.0031 | 2.38 | ( 1.31, 4.31) | 2.42 | (1.32, 4.42) | 0.02 | ( 0.01, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7576 |
| <130 | 1684 | 14 | 0.8 | 1687 | 36 | 2.1 | 0.0019 | 2.55 | ( 1.38, 4.70) | 2.58 | (1.39, 4.81) | 0.01 | ( 0.00, 0.02) | |
| >=130 | 1591 | 14 | 0.9 | 1643 | 32 | 1.9 | 0.0102 | 2.22 | ( 1.19, 4.14) | 2.24 | (1.19, 4.22) | 0.01 | ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3581 |
| <75 | 1653 | 17 | 1.0 | 1612 | 29 | 1.8 | 0.0645 | 1.74 | ( 0.96, 3.15) | 1.75 | (0.96, 3.21) | 0.01 | ( 0.00, 0.02) | |
| 75 to <85 | 1005 | 6 | 0.6 | 1085 | 20 | 1.8 | 0.0119 | 2.93 | ( 1.22, 7.06) | 2.97 | (1.22, 7.21) | 0.01 | ( 0.00, 0.02) | |
| >=85 | 617 | 5 | 0.8 | 633 | 19 | 3.0 | 0.0047 | 3.71 | ( 1.40, 9.86) | 3.79 | (1.41,10.20) | 0.02 | ( 0.01, 0.04) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8253 |
| <30 | 250 | 2 | 0.8 | 263 | 4 | 1.5 | 0.4556 | 1.79 | ( 0.38, 8.42) | 1.80 | (0.38, 8.63) | 0.01 | (-0.01, 0.03) | |
| 30 to <45 | 898 | 6 | 0.7 | 909 | 18 | 2.0 | 0.0149 | 2.96 | ( 1.18, 7.40) | 2.99 | (1.18, 7.57) | 0.01 | ( 0.00, 0.02) | |
| >=45 | 2126 | 20 | 0.9 | 2158 | 46 | 2.1 | 0.0017 | 2.25 | ( 1.34, 3.80) | 2.28 | (1.34, 3.87) | 0.01 | ( 0.00, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7371 |
| Normal (<30) | 1216 | 8 | 0.7 | 1243 | 25 | 2.0 | 0.0036 | 3.05 | ( 1.38, 6.74) | 3.09 | (1.39, 6.89) | 0.01 | ( 0.00, 0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 15 | 1.0 | 1546 | 33 | 2.1 | 0.0092 | 2.19 | ( 1.20, 4.01) | 2.22 | (1.20, 4.10) | 0.01 | ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 500 | 5 | 1.0 | 525 | 10 | 1.9 | 0.2220 | 1.92 | ( 0.66, 5.55) | 1.93 | (0.66, 5.69) | 0.01 | (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8666 |
| Low, moderate or high | 2430 | 22 | 0.9 | 2495 | 53 | 2.1 | 0.0005 | 2.33 | ( 1.42, 3.82) | 2.36 | (1.43, 3.90) | 0.01 | ( 0.01, 0.02) | |
| Very high | 834 | 6 | 0.7 | 820 | 15 | 1.8 | 0.0438 | 2.56 | ( 0.99, 6.60) | 2.58 | (1.00, 6.71) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3944 |
| No | 572 | 6 | 1.0 | 578 | 10 | 1.7 | 0.3311 | 1.61 | ( 0.61, 4.26) | 1.62 | (0.61, 4.36) | 0.01 | (-0.01, 0.02) | |
| Yes | 2703 | 22 | 0.8 | 2752 | 58 | 2.1 | <0.0001 | 2.58 | ( 1.59, 4.21) | 2.62 | (1.60, 4.29) | 0.01 | ( 0.01, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7867 |
| No | 344 | 1 | 0.3 | 349 | 5 | 1.4 | 0.1651 | 2.86 | ( 0.60,13.49) | 2.87 | (0.59,14.01) | 0.01 | ( 0.00, 0.03) | |
| Yes | 2931 | 27 | 0.9 | 2981 | 63 | 2.1 | 0.0002 | 2.28 | ( 1.46, 3.57) | 2.31 | (1.47, 3.64) | 0.01 | ( 0.01, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.9995 |
| No | 275 | 3 | 1.1 | 307 | 8 | 2.6 | 0.1812 | 2.37 ( 0.64, 8.79) | 2.41 (0.64, 9.13) | 0.02 (-0.01, 0.04) | |
| Yes | 3000 | 25 | 0.8 | 3023 | 60 | 2.0 | 0.0002 | 2.38 ( 1.49, 3.78) | 2.41 (1.50, 3.85) | 0.01 ( 0.01, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 22 | 0.7 | 3330 | 32 | 1.0 | 0.1963 | 1.43 | ( 0.83, 2.45) | 1.43 | (0.83, 2.47) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.4806 |
| 1245.110 | 2001 | 16 | 0.8 | 2052 | 26 | 1.3 | 0.1418 | 1.58 | ( 0.85, 2.94) | 1.59 | (0.85, 2.98) | 0.00 | ( 0.00, 0.01) | |
| 1245.121 | 1274 | 6 | 0.5 | 1278 | 6 | 0.5 | 0.9957 | 1.00 | ( 0.32, 3.08) | 1.00 | (0.32, 3.10) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0581 |
| Male | 2023 | 14 | 0.7 | 2068 | 12 | 0.6 | 0.6490 | 0.84 | ( 0.39, 1.80) | 0.84 | (0.39, 1.81) | 0.00 | (-0.01, 0.00) | |
| Female | 1252 | 8 | 0.6 | 1262 | 20 | 1.6 | 0.0242 | 2.47 | ( 1.09, 5.58) | 2.49 | (1.10, 5.68) | 0.01 | ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.4433 |
| <65 | 766 | 3 | 0.4 | 705 | 2 | 0.3 | 0.7240 | 0.73 | ( 0.12, 4.34) | 0.72 | (0.12, 4.36) | 0.00 | (-0.01, 0.00) | |
| >=65 | 2509 | 19 | 0.8 | 2625 | 30 | 1.1 | 0.1532 | 1.51 | ( 0.85, 2.68) | 1.52 | (0.85, 2.71) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.9404 |
| North America | 434 | 3 | 0.7 | 432 | 5 | 1.2 | 0.4751 | 1.67 | ( 0.40, 6.96) | 1.68 | (0.40, 7.08) | 0.00 | (-0.01, 0.02) | |
| Latin America | 931 | 5 | 0.5 | 944 | 7 | 0.7 | 0.5700 | 1.39 | ( 0.44, 4.36) | 1.39 | (0.44, 4.40) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 10 | 0.7 | 1361 | 11 | 0.8 | 0.8700 | 1.07 | ( 0.46, 2.52) | 1.07 | (0.45, 2.54) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 2 | 0.5 | 413 | 5 | 1.2 | 0.3130 | 2.14 | ( 0.47, 9.71) | 2.15 | (0.47, 9.74) | 0.01 | (-0.01, 0.02) | |
| Other | 171 | 2 | 1.2 | 180 | 4 | 2.2 | 0.5050 | 1.68 | ( 0.36, 7.79) | 1.70 | (0.35, 8.10) | 0.01 | (-0.02, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8149 |
| Diabetic | 1739 | 13 | 0.7 | 1779 | 18 | 1.0 | 0.4092 | 1.35 | ( 0.66, 2.75) | 1.35 | (0.66, 2.77) | 0.00 | ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 9 | 0.6 | 1551 | 14 | 0.9 | 0.3090 | 1.54 | ( 0.67, 3.54) | 1.54 | (0.67, 3.57) | 0.00 | ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1044 |
| <30 | 1975 | 15 | 0.8 | 1930 | 14 | 0.7 | 0.8718 | 0.94 | ( 0.46, 1.94) | 0.94 | (0.45, 1.96) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1300 | 7 | 0.5 | 1400 | 18 | 1.3 | 0.0404 | 2.40 | ( 1.01, 5.69) | 2.41 | (1.01, 5.77) | 0.01 | ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5945 |
| <130 | 1684 | 12 | 0.7 | 1687 | 15 | 0.9 | 0.5939 | 1.23 | ( 0.58, 2.61) | 1.23 | (0.57, 2.64) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 1591 | 10 | 0.6 | 1643 | 17 | 1.0 | 0.2028 | 1.65 | ( 0.76, 3.58) | 1.65 | (0.76, 3.62) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3927 |
| <75 | 1653 | 13 | 0.8 | 1612 | 12 | 0.7 | 0.8829 | 0.94 | ( 0.43, 2.06) | 0.94 | (0.43, 2.07) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 5 | 0.5 | 1085 | 12 | 1.1 | 0.1322 | 2.12 | ( 0.78, 5.75) | 2.13 | (0.78, 5.84) | 0.01 | ( 0.00, 0.01) | |
| >=85 | 617 | 4 | 0.6 | 633 | 8 | 1.3 | 0.2801 | 1.85 | ( 0.59, 5.75) | 1.86 | (0.59, 5.86) | 0.01 | (-0.01, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8169 |
| <30 | 250 | 4 | 1.6 | 263 | 6 | 2.3 | 0.5500 | 1.45 | ( 0.43, 4.87) | 1.46 | (0.43, 4.98) | 0.01 | (-0.02, 0.03) | |
| 30 to <45 | 898 | 10 | 1.1 | 909 | 12 | 1.3 | 0.7088 | 1.17 | ( 0.52, 2.64) | 1.17 | (0.51, 2.68) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 8 | 0.4 | 2158 | 14 | 0.6 | 0.2159 | 1.72 | ( 0.72, 4.09) | 1.72 | (0.72, 4.12) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9069 |
| Normal (<30) | 1216 | 7 | 0.6 | 1243 | 12 | 1.0 | 0.2746 | 1.67 | ( 0.66, 4.22) | 1.68 | (0.66, 4.28) | 0.00 | ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 10 | 0.6 | 1546 | 15 | 1.0 | 0.3186 | 1.50 | ( 0.67, 3.32) | 1.50 | (0.67, 3.35) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 500 | 4 | 0.8 | 525 | 5 | 1.0 | 0.7943 | 1.18 | ( 0.34, 4.05) | 1.18 | (0.34, 4.12) | 0.00 | (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5380 |
| Low, moderate or high | 2430 | 9 | 0.4 | 2495 | 17 | 0.7 | 0.1376 | 1.82 | ( 0.82, 4.08) | 1.83 | (0.81, 4.12) | 0.00 | ( 0.00, 0.01) | |
| Very high | 834 | 12 | 1.4 | 820 | 15 | 1.8 | 0.5037 | 1.29 | ( 0.61, 2.73) | 1.30 | (0.60, 2.79) | 0.00 | (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1733 |
| No | 572 | 2 | 0.3 | 578 | 8 | 1.4 | 0.0707 | 3.38 | ( 0.83,13.77) | 3.42 | (0.83,14.06) | 0.01 | ( 0.00, 0.02) | |
| Yes | 2703 | 20 | 0.7 | 2752 | 24 | 0.9 | 0.5978 | 1.17 | ( 0.65, 2.12) | 1.17 | (0.65, 2.13) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6702 |
| No | 344 | 3 | 0.9 | 349 | 6 | 1.7 | 0.3520 | 1.81 | ( 0.51, 6.48) | 1.83 | (0.50, 6.68) | 0.01 | (-0.01, 0.03) | |
| Yes | 2931 | 19 | 0.6 | 2981 | 26 | 0.9 | 0.3319 | 1.34 | ( 0.74, 2.41) | 1.34 | (0.74, 2.43) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.1488 |
| No | 275 | 3 | 1.1 | 307 | 1 | 0.3 | 0.2922 | 0.37 ( 0.06, 2.50) | 0.37 (0.05, 2.53) | -0.01 (-0.02, 0.01) | |
| Yes | 3000 | 19 | 0.6 | 3023 | 31 | 1.0 | 0.0963 | 1.61 ( 0.91, 2.85) | 1.62 (0.91, 2.87) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 148 | 4.5 | 3330 | 159 | 4.8 | 0.6405 | 1.05 | ( 0.85, 1.31) | 1.06 | (0.84, 1.33) | 0.00 | (-0.01, 0.01) | |
| Study | | | | | | | | | | | | | | 0.7778 |
| 1245.110 | 2001 | 110 | 5.5 | 2052 | 121 | 5.9 | 0.5835 | 1.07 | ( 0.83, 1.38) | 1.08 | (0.83, 1.41) | 0.00 | (-0.01, 0.02) | |
| 1245.121 | 1274 | 38 | 3.0 | 1278 | 38 | 3.0 | 0.9889 | 1.00 | ( 0.64, 1.55) | 1.00 | (0.63, 1.57) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.8665 |
| Male | 2023 | 70 | 3.5 | 2068 | 74 | 3.6 | 0.8411 | 1.03 | ( 0.75, 1.42) | 1.03 | (0.74, 1.44) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 78 | 6.2 | 1262 | 85 | 6.7 | 0.6425 | 1.07 | ( 0.80, 1.44) | 1.08 | (0.78, 1.48) | 0.00 | (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.3012 |
| <65 | 766 | 19 | 2.5 | 705 | 13 | 1.8 | 0.3859 | 0.74 | ( 0.37, 1.48) | 0.73 | (0.36, 1.49) | -0.01 | (-0.02, 0.01) | |
| >=65 | 2509 | 129 | 5.1 | 2625 | 146 | 5.6 | 0.4956 | 1.08 | ( 0.86, 1.36) | 1.09 | (0.85, 1.39) | 0.00 | (-0.01, 0.02) | |
| Region | | | | | | | | | | | | | | 0.2624 |
| North America | 434 | 29 | 6.7 | 432 | 23 | 5.3 | 0.3960 | 0.80 | ( 0.47, 1.35) | 0.78 | (0.45, 1.38) | -0.01 | (-0.05, 0.02) | |
| Latin America | 931 | 26 | 2.8 | 944 | 22 | 2.3 | 0.5493 | 0.84 | ( 0.48, 1.47) | 0.84 | (0.47, 1.49) | 0.00 | (-0.02, 0.01) | |
| Europe | 1334 | 62 | 4.6 | 1361 | 63 | 4.6 | 0.9674 | 0.99 | ( 0.71, 1.40) | 0.99 | (0.69, 1.42) | 0.00 | (-0.02, 0.02) | |
| Asia | 405 | 24 | 5.9 | 413 | 41 | 9.9 | 0.0423 | 1.64 | ( 1.01, 2.65) | 1.72 | (1.01, 2.91) | 0.04 | ( 0.00, 0.07) | |
| Other | 171 | 7 | 4.1 | 180 | 10 | 5.6 | 0.5578 | 1.32 | ( 0.52, 3.40) | 1.35 | (0.50, 3.63) | 0.01 | (-0.03, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9989 |
| Diabetic | 1739 | 73 | 4.2 | 1779 | 79 | 4.4 | 0.7396 | 1.05 | ( 0.77, 1.44) | 1.06 | (0.76, 1.46) | 0.00 | (-0.01, 0.02) | |
| Non-Diabetic | 1536 | 75 | 4.9 | 1551 | 80 | 5.2 | 0.7370 | 1.05 | ( 0.78, 1.43) | 1.06 | (0.76, 1.46) | 0.00 | (-0.01, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8429 |
| <30 | 1975 | 98 | 5.0 | 1930 | 101 | 5.2 | 0.7483 | 1.05 | ( 0.80, 1.37) | 1.05 | (0.79, 1.39) | 0.00 | (-0.01, 0.02) | |
| >=30 | 1300 | 50 | 3.8 | 1400 | 58 | 4.1 | 0.6308 | 1.09 | ( 0.76, 1.58) | 1.10 | (0.75, 1.62) | 0.00 | (-0.01, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7615 |
| <130 | 1684 | 67 | 4.0 | 1687 | 74 | 4.4 | 0.5955 | 1.09 | ( 0.79, 1.51) | 1.10 | (0.78, 1.54) | 0.00 | (-0.01, 0.02) | |
| >=130 | 1591 | 81 | 5.1 | 1643 | 85 | 5.2 | 0.8968 | 1.02 | ( 0.76, 1.37) | 1.02 | (0.75, 1.40) | 0.00 | (-0.01, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8223 |
| <75 | 1653 | 82 | 5.0 | 1612 | 87 | 5.4 | 0.6072 | 1.08 | ( 0.81, 1.45) | 1.08 | (0.80, 1.48) | 0.00 | (-0.01, 0.02) | |
| 75 to <85 | 1005 | 41 | 4.1 | 1085 | 49 | 4.5 | 0.6108 | 1.11 | ( 0.74, 1.67) | 1.12 | (0.73, 1.71) | 0.00 | (-0.01, 0.02) | |
| >=85 | 617 | 25 | 4.1 | 633 | 23 | 3.6 | 0.7162 | 0.90 | ( 0.52, 1.57) | 0.90 | (0.50, 1.60) | 0.00 | (-0.03, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7964 |
| <30 | 250 | 11 | 4.4 | 263 | 14 | 5.3 | 0.5558 | 1.26 | ( 0.59, 2.68) | 1.27 | (0.57, 2.84) | 0.01 | (-0.03, 0.05) | |
| 30 to <45 | 898 | 53 | 5.9 | 909 | 52 | 5.7 | 0.8484 | 0.96 | ( 0.67, 1.40) | 0.96 | (0.65, 1.43) | 0.00 | (-0.02, 0.02) | |
| >=45 | 2126 | 84 | 4.0 | 2158 | 93 | 4.3 | 0.5944 | 1.08 | ( 0.81, 1.44) | 1.09 | (0.80, 1.47) | 0.00 | (-0.01, 0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.0726 |
| Normal (<30) | 1216 | 63 | 5.2 | 1243 | 50 | 4.0 | 0.1654 | 0.77 | ( 0.54, 1.11) | 0.76 | (0.52, 1.12) | -0.01 | (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 63 | 4.1 | 1546 | 86 | 5.6 | 0.0580 | 1.36 | ( 0.99, 1.86) | 1.38 | (0.99, 1.93) | 0.01 | ( 0.00, 0.03) | |
| Macroalbuminuria (>300) | 500 | 21 | 4.2 | 525 | 22 | 4.2 | 0.9821 | 1.01 | ( 0.56, 1.80) | 1.01 | (0.55, 1.86) | 0.00 | (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7633 |
| Low, moderate or high | 2430 | 102 | 4.2 | 2495 | 110 | 4.4 | 0.7523 | 1.04 | ( 0.80, 1.36) | 1.05 | (0.79, 1.38) | 0.00 | (-0.01, 0.01) | |
| Very high | 834 | 45 | 5.4 | 820 | 49 | 6.0 | 0.5651 | 1.12 | ( 0.76, 1.66) | 1.13 | (0.74, 1.72) | 0.01 | (-0.02, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2668 |
| No | 572 | 37 | 6.5 | 578 | 48 | 8.3 | 0.2300 | 1.29 | ( 0.85, 1.95) | 1.31 | (0.84, 2.05) | 0.02 | (-0.01, 0.05) | |
| Yes | 2703 | 111 | 4.1 | 2752 | 111 | 4.0 | 0.8586 | 0.98 | ( 0.76, 1.26) | 0.98 | (0.75, 1.28) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3415 |
| No | 344 | 20 | 5.8 | 349 | 16 | 4.6 | 0.4572 | 0.78 | ( 0.41, 1.49) | 0.77 | (0.39, 1.52) | -0.01 | (-0.05, 0.02) | |
| Yes | 2931 | 128 | 4.4 | 2981 | 143 | 4.8 | 0.4576 | 1.09 | ( 0.87, 1.38) | 1.10 | (0.86, 1.40) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.8086 |
| No | 275 | 14 | 5.1 | 307 | 15 | 4.9 | 0.9345 | 0.97 ( 0.49, 1.94) | 0.97 (0.46, 2.02) | 0.00 (-0.04, 0.03) | |
| Yes | 3000 | 134 | 4.5 | 3023 | 144 | 4.8 | 0.6006 | 1.06 ( 0.85, 1.34) | 1.07 (0.84, 1.36) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 19 | 0.6 | 3330 | 25 | 0.8 | 0.3960 | 1.29 | ( 0.71, 2.34) | 1.29 | (0.71, 2.36) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.7328 |
| 1245.110 | 2001 | 13 | 0.6 | 2052 | 16 | 0.8 | 0.6234 | 1.20 | ( 0.58, 2.49) | 1.20 | (0.58, 2.50) | 0.00 | ( 0.00, 0.01) | |
| 1245.121 | 1274 | 6 | 0.5 | 1278 | 9 | 0.7 | 0.4409 | 1.50 | ( 0.53, 4.19) | 1.50 | (0.53, 4.22) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.8132 |
| Male | 2023 | 13 | 0.6 | 2068 | 18 | 0.9 | 0.4021 | 1.35 | ( 0.67, 2.75) | 1.36 | (0.66, 2.78) | 0.00 | ( 0.00, 0.01) | |
| Female | 1252 | 6 | 0.5 | 1262 | 7 | 0.6 | 0.7935 | 1.16 | ( 0.39, 3.44) | 1.16 | (0.39, 3.46) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.2981 |
| <65 | 766 | 4 | 0.5 | 705 | 2 | 0.3 | 0.5174 | 0.61 | ( 0.13, 2.81) | 0.60 | (0.13, 2.83) | 0.00 | (-0.01, 0.00) | |
| >=65 | 2509 | 15 | 0.6 | 2625 | 23 | 0.9 | 0.2440 | 1.47 | ( 0.77, 2.80) | 1.47 | (0.77, 2.83) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.8949 |
| North America | 434 | 4 | 0.9 | 432 | 3 | 0.7 | 0.7115 | 0.76 | ( 0.17, 3.35) | 0.75 | (0.17, 3.39) | 0.00 | (-0.01, 0.01) | |
| Latin America | 931 | 1 | 0.1 | 944 | 3 | 0.3 | 0.3768 | 2.31 | ( 0.34,15.66) | 2.32 | (0.34,15.75) | 0.00 | ( 0.00, 0.01) | |
| Europe | 1334 | 11 | 0.8 | 1361 | 13 | 1.0 | 0.7164 | 1.16 | ( 0.52, 2.58) | 1.16 | (0.52, 2.60) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 2 | 0.5 | 413 | 4 | 1.0 | 0.4767 | 1.73 | ( 0.37, 8.03) | 1.74 | (0.37, 8.20) | 0.00 | (-0.01, 0.02) | |
| Other | 171 | 1 | 0.6 | 180 | 2 | 1.1 | 0.6556 | 1.58 | ( 0.21,11.95) | 1.59 | (0.21,12.21) | 0.01 | (-0.02, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8173 |
| Diabetic | 1739 | 12 | 0.7 | 1779 | 15 | 0.8 | 0.6023 | 1.22 | ( 0.57, 2.60) | 1.22 | (0.57, 2.62) | 0.00 | ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 7 | 0.5 | 1551 | 10 | 0.6 | 0.4808 | 1.41 | ( 0.54, 3.70) | 1.41 | (0.54, 3.73) | 0.00 | ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4116 |
| <30 | 1975 | 11 | 0.6 | 1930 | 17 | 0.9 | 0.2289 | 1.58 | ( 0.74, 3.37) | 1.59 | (0.74, 3.40) | 0.00 | ( 0.00, 0.01) | |
| >=30 | 1300 | 8 | 0.6 | 1400 | 8 | 0.6 | 0.9083 | 0.94 | ( 0.36, 2.51) | 0.94 | (0.35, 2.52) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8579 |
| <130 | 1684 | 9 | 0.5 | 1687 | 11 | 0.7 | 0.6616 | 1.22 | ( 0.50, 2.94) | 1.22 | (0.50, 2.95) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 1591 | 10 | 0.6 | 1643 | 14 | 0.9 | 0.4581 | 1.36 | ( 0.60, 3.05) | 1.36 | (0.60, 3.07) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2844 |
| <75 | 1653 | 10 | 0.6 | 1612 | 15 | 0.9 | 0.2878 | 1.53 | ( 0.69, 3.40) | 1.54 | (0.69, 3.43) | 0.00 | ( 0.00, 0.01) | |
| 75 to <85 | 1005 | 4 | 0.4 | 1085 | 8 | 0.7 | 0.3031 | 1.86 | ( 0.56, 6.15) | 1.86 | (0.56, 6.21) | 0.00 | ( 0.00, 0.01) | |
| >=85 | 617 | 5 | 0.8 | 633 | 2 | 0.3 | 0.2709 | 0.44 | ( 0.10, 1.96) | 0.44 | (0.10, 1.97) | 0.00 | (-0.01, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9911 |
| <30 | 250 | 2 | 0.8 | 263 | 3 | 1.1 | 0.7064 | 1.35 | ( 0.29, 6.35) | 1.35 | (0.27, 6.68) | 0.00 | (-0.02, 0.02) | |
| 30 to <45 | 898 | 2 | 0.2 | 909 | 3 | 0.3 | 0.6953 | 1.38 | ( 0.27, 6.95) | 1.38 | (0.27, 7.01) | 0.00 | ( 0.00, 0.01) | |
| >=45 | 2126 | 15 | 0.7 | 2158 | 19 | 0.9 | 0.5194 | 1.25 | ( 0.64, 2.45) | 1.25 | (0.63, 2.46) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6330 |
| Normal (<30) | 1216 | 10 | 0.8 | 1243 | 10 | 0.8 | 0.9529 | 0.97 | ( 0.42, 2.28) | 0.97 | (0.41, 2.30) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 6 | 0.4 | 1546 | 11 | 0.7 | 0.2203 | 1.85 | ( 0.68, 5.00) | 1.85 | (0.68, 5.03) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 500 | 3 | 0.6 | 525 | 4 | 0.8 | 0.7660 | 1.25 | ( 0.28, 5.54) | 1.26 | (0.28, 5.63) | 0.00 | (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2400 |
| Low, moderate or high | 2430 | 17 | 0.7 | 2495 | 19 | 0.8 | 0.8052 | 1.09 | ( 0.57, 2.08) | 1.09 | (0.56, 2.09) | 0.00 | ( 0.00, 0.01) | |
| Very high | 834 | 2 | 0.2 | 820 | 6 | 0.7 | 0.1492 | 3.04 | ( 0.62,14.96) | 3.06 | (0.62,15.16) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1403 |
| No | 572 | 1 | 0.2 | 578 | 6 | 1.0 | 0.0797 | 4.27 | ( 0.73,25.16) | 4.31 | (0.73,25.56) | 0.01 | ( 0.00, 0.02) | |
| Yes | 2703 | 18 | 0.7 | 2752 | 19 | 0.7 | 0.9170 | 1.03 | ( 0.54, 1.97) | 1.03 | (0.54, 1.98) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1122 |
| No | 344 | 4 | 1.2 | 349 | 1 | 0.3 | 0.2019 | 0.31 | ( 0.05, 2.05) | 0.31 | (0.05, 2.03) | -0.01 | (-0.02, 0.00) | |
| Yes | 2931 | 15 | 0.5 | 2981 | 24 | 0.8 | 0.1663 | 1.57 | ( 0.82, 2.98) | 1.57 | (0.82, 3.01) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6515 |
| No | 275 | 2 | 0.7 | 307 | 2 | 0.7 | 0.8781 | 0.87 | ( 0.15, 5.09) | 0.87 | (0.15, 5.12) | 0.00 | (-0.02, 0.01) | |
| Yes | 3000 | 17 | 0.6 | 3023 | 23 | 0.8 | 0.3558 | 1.34 | ( 0.72, 2.50) | 1.34 | (0.72, 2.52) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 391 | 11.9 | 3330 | 449 | 13.5 | 0.0600 | 1.13 | ( 0.99, 1.28) | 1.15 | (0.99, 1.33) | 0.02 | ( 0.00, 0.03) | |
| Study | | | | | | | | | | | | | | 0.0417 |
| 1245.110 | 2001 | 229 | 11.4 | 2052 | 294 | 14.3 | 0.0062 | 1.25 | ( 1.07, 1.47) | 1.29 | (1.08, 1.56) | 0.03 | ( 0.01, 0.05) | |
| 1245.121 | 1274 | 162 | 12.7 | 1278 | 155 | 12.1 | 0.6528 | 0.95 | ( 0.78, 1.17) | 0.95 | (0.75, 1.20) | -0.01 | (-0.03, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.3955 |
| Male | 2023 | 246 | 12.2 | 2068 | 272 | 13.2 | 0.3406 | 1.08 | ( 0.92, 1.27) | 1.09 | (0.91, 1.32) | 0.01 | (-0.01, 0.03) | |
| Female | 1252 | 145 | 11.6 | 1262 | 177 | 14.0 | 0.0669 | 1.21 | ( 0.99, 1.49) | 1.25 | (0.98, 1.58) | 0.02 | ( 0.00, 0.05) | |
| Age [years] | | | | | | | | | | | | | | 0.6111 |
| <65 | 766 | 78 | 10.2 | 705 | 75 | 10.6 | 0.7592 | 1.05 | ( 0.78, 1.42) | 1.05 | (0.75, 1.47) | 0.00 | (-0.03, 0.04) | |
| >=65 | 2509 | 313 | 12.5 | 2625 | 374 | 14.2 | 0.0619 | 1.14 | ( 0.99, 1.31) | 1.17 | (0.99, 1.37) | 0.02 | ( 0.00, 0.04) | |
| Region | | | | | | | | | | | | | | 0.2389 |
| North America | 434 | 88 | 20.3 | 432 | 96 | 22.2 | 0.4810 | 1.10 | ( 0.85, 1.42) | 1.12 | (0.81, 1.56) | 0.02 | (-0.03, 0.07) | |
| Latin America | 931 | 87 | 9.3 | 944 | 102 | 10.8 | 0.2995 | 1.15 | ( 0.88, 1.51) | 1.17 | (0.87, 1.58) | 0.01 | (-0.01, 0.04) | |
| Europe | 1334 | 153 | 11.5 | 1361 | 157 | 11.5 | 0.9647 | 1.00 | ( 0.81, 1.24) | 1.01 | (0.79, 1.27) | 0.00 | (-0.02, 0.02) | |
| Asia | 405 | 47 | 11.6 | 413 | 60 | 14.5 | 0.2210 | 1.25 | ( 0.87, 1.78) | 1.29 | (0.86, 1.94) | 0.03 | (-0.02, 0.08) | |
| Other | 171 | 16 | 9.4 | 180 | 34 | 18.9 | 0.0129 | 1.98 | ( 1.14, 3.45) | 2.23 | (1.17, 4.22) | 0.09 | ( 0.02, 0.16) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5120 |
| Diabetic | 1739 | 196 | 11.3 | 1779 | 236 | 13.3 | 0.0713 | 1.18 | ( 0.99, 1.41) | 1.20 | (0.98, 1.47) | 0.02 | ( 0.00, 0.04) | |
| Non-Diabetic | 1536 | 195 | 12.7 | 1551 | 213 | 13.7 | 0.3968 | 1.08 | ( 0.90, 1.30) | 1.09 | (0.89, 1.35) | 0.01 | (-0.01, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3772 |
| <30 | 1975 | 228 | 11.5 | 1930 | 264 | 13.7 | 0.0447 | 1.18 | (>1.00, 1.40) | 1.21 | (1.00, 1.47) | 0.02 | ( 0.00, 0.04) | |
| >=30 | 1300 | 163 | 12.5 | 1400 | 185 | 13.2 | 0.5903 | 1.06 | ( 0.87, 1.28) | 1.06 | (0.85, 1.33) | 0.01 | (-0.02, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7908 |
| <130 | 1684 | 237 | 14.1 | 1687 | 273 | 16.2 | 0.0899 | 1.15 | ( 0.98, 1.35) | 1.18 | (0.97, 1.42) | 0.02 | ( 0.00, 0.05) | |
| >=130 | 1591 | 154 | 9.7 | 1643 | 176 | 10.7 | 0.3212 | 1.11 | ( 0.90, 1.36) | 1.12 | (0.89, 1.41) | 0.01 | (-0.01, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8747 |
| <75 | 1653 | 232 | 14.0 | 1612 | 256 | 15.9 | 0.1395 | 1.13 | ( 0.96, 1.33) | 1.16 | (0.95, 1.40) | 0.02 | (-0.01, 0.04) | |
| 75 to <85 | 1005 | 105 | 10.4 | 1085 | 125 | 11.5 | 0.4314 | 1.10 | ( 0.86, 1.41) | 1.12 | (0.85, 1.47) | 0.01 | (-0.02, 0.04) | |
| >=85 | 617 | 54 | 8.8 | 633 | 68 | 10.7 | 0.2304 | 1.23 | ( 0.88, 1.73) | 1.26 | (0.86, 1.83) | 0.02 | (-0.01, 0.05) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0084 |
| <30 | 250 | 37 | 14.8 | 263 | 50 | 19.0 | 0.2206 | 1.27 | ( 0.87, 1.87) | 1.33 | (0.84, 2.12) | 0.04 | (-0.02, 0.11) | |
| 30 to <45 | 898 | 145 | 16.1 | 909 | 124 | 13.6 | 0.1320 | 0.84 | ( 0.68, 1.05) | 0.82 | (0.63, 1.06) | -0.03 | (-0.06, 0.01) | |
| >=45 | 2126 | 209 | 9.8 | 2158 | 275 | 12.7 | 0.0026 | 1.30 | ( 1.09, 1.54) | 1.34 | (1.11, 1.62) | 0.03 | ( 0.01, 0.05) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1540 |
| Normal (<30) | 1216 | 160 | 13.2 | 1243 | 188 | 15.1 | 0.1644 | 1.15 | ( 0.94, 1.40) | 1.18 | (0.94, 1.48) | 0.02 | (-0.01, 0.05) | |
| Microalbuminuria (30 to <=300) | 1548 | 175 | 11.3 | 1546 | 213 | 13.8 | 0.0373 | 1.22 | ( 1.01, 1.47) | 1.25 | (1.01, 1.55) | 0.02 | ( 0.00, 0.05) | |
| Macroalbuminuria (>300) | 500 | 55 | 11.0 | 525 | 47 | 9.0 | 0.2683 | 0.81 | ( 0.56, 1.17) | 0.79 | (0.53, 1.20) | -0.02 | (-0.06, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2857 |
| Low, moderate or high | 2430 | 270 | 11.1 | 2495 | 328 | 13.1 | 0.0296 | 1.18 | ( 1.02, 1.38) | 1.21 | (1.02, 1.44) | 0.02 | ( 0.00, 0.04) | |
| Very high | 834 | 120 | 14.4 | 820 | 120 | 14.6 | 0.8941 | 1.02 | ( 0.80, 1.28) | 1.02 | (0.78, 1.34) | 0.00 | (-0.03, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4989 |
| No | 572 | 74 | 12.9 | 578 | 77 | 13.3 | 0.8528 | 1.03 | ( 0.76, 1.38) | 1.03 | (0.73, 1.45) | 0.00 | (-0.04, 0.04) | |
| Yes | 2703 | 317 | 11.7 | 2752 | 372 | 13.5 | 0.0475 | 1.15 | (>1.00, 1.33) | 1.18 | (1.00, 1.38) | 0.02 | ( 0.00, 0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8846 |
| No | 344 | 39 | 11.3 | 349 | 46 | 13.2 | 0.4633 | 1.16 | ( 0.78, 1.73) | 1.19 | (0.75, 1.87) | 0.02 | (-0.03, 0.07) | |
| Yes | 2931 | 352 | 12.0 | 2981 | 403 | 13.5 | 0.0833 | 1.13 | ( 0.98, 1.29) | 1.14 | (0.98, 1.33) | 0.02 | ( 0.00, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.9577 |
| No | 275 | 20 | 7.3 | 307 | 25 | 8.1 | 0.7025 | 1.12 ( 0.64, 1.96) | 1.13 (0.61, 2.07) | 0.01 (-0.03, 0.05) | |
| Yes | 3000 | 371 | 12.4 | 3023 | 424 | 14.0 | 0.0580 | 1.13 (<1.00, 1.29) | 1.16 (1.00, 1.34) | 0.02 ( 0.00, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 348 | 10.6 | 3330 | 389 | 11.7 | 0.1735 | 1.10 | ( 0.96, 1.26) | 1.11 | (0.95, 1.30) | 0.01 | ( 0.00, 0.03) | |
| Study | | | | | | | | | | | | | | 0.1117 |
| 1245.110 | 2001 | 204 | 10.2 | 2052 | 251 | 12.2 | 0.0400 | 1.20 | ( 1.01, 1.43) | 1.23 | (1.01, 1.49) | 0.02 | ( 0.00, 0.04) | |
| 1245.121 | 1274 | 144 | 11.3 | 1278 | 138 | 10.8 | 0.6843 | 0.96 | ( 0.77, 1.19) | 0.95 | (0.74, 1.22) | -0.01 | (-0.03, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.5363 |
| Male | 2023 | 219 | 10.8 | 2068 | 238 | 11.5 | 0.4886 | 1.06 | ( 0.89, 1.26) | 1.07 | (0.88, 1.30) | 0.01 | (-0.01, 0.03) | |
| Female | 1252 | 129 | 10.3 | 1262 | 151 | 12.0 | 0.1849 | 1.16 | ( 0.93, 1.45) | 1.18 | (0.92, 1.52) | 0.02 | (-0.01, 0.04) | |
| Age [years] | | | | | | | | | | | | | | 0.8737 |
| <65 | 766 | 70 | 9.1 | 705 | 72 | 10.2 | 0.4735 | 1.12 | ( 0.82, 1.53) | 1.14 | (0.80, 1.61) | 0.01 | (-0.02, 0.04) | |
| >=65 | 2509 | 278 | 11.1 | 2625 | 317 | 12.1 | 0.2642 | 1.09 | ( 0.94, 1.27) | 1.10 | (0.93, 1.31) | 0.01 | (-0.01, 0.03) | |
| Region | | | | | | | | | | | | | | 0.1498 |
| North America | 434 | 81 | 18.7 | 432 | 87 | 20.1 | 0.5815 | 1.08 | ( 0.82, 1.42) | 1.10 | (0.78, 1.54) | 0.01 | (-0.04, 0.07) | |
| Latin America | 931 | 79 | 8.5 | 944 | 96 | 10.2 | 0.2161 | 1.20 | ( 0.90, 1.59) | 1.22 | (0.89, 1.66) | 0.02 | (-0.01, 0.04) | |
| Europe | 1334 | 142 | 10.6 | 1361 | 137 | 10.1 | 0.6172 | 0.94 | ( 0.76, 1.18) | 0.94 | (0.73, 1.20) | -0.01 | (-0.03, 0.02) | |
| Asia | 405 | 33 | 8.1 | 413 | 39 | 9.4 | 0.5030 | 1.16 | ( 0.75, 1.81) | 1.18 | (0.73, 1.92) | 0.01 | (-0.03, 0.05) | |
| Other | 171 | 13 | 7.6 | 180 | 30 | 16.7 | 0.0117 | 2.13 | ( 1.16, 3.93) | 2.40 | (1.20, 4.80) | 0.09 | ( 0.02, 0.15) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3793 |
| Diabetic | 1739 | 169 | 9.7 | 1779 | 202 | 11.4 | 0.1131 | 1.17 | ( 0.96, 1.42) | 1.19 | (0.96, 1.48) | 0.02 | ( 0.00, 0.04) | |
| Non-Diabetic | 1536 | 179 | 11.7 | 1551 | 187 | 12.1 | 0.7319 | 1.03 | ( 0.85, 1.25) | 1.04 | (0.84, 1.29) | 0.00 | (-0.02, 0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5264 |
| <30 | 1975 | 201 | 10.2 | 1930 | 224 | 11.6 | 0.1491 | 1.14 | ( 0.95, 1.37) | 1.16 | (0.95, 1.42) | 0.01 | (-0.01, 0.03) | |
| >=30 | 1300 | 147 | 11.3 | 1400 | 165 | 11.8 | 0.6845 | 1.04 | ( 0.85, 1.29) | 1.05 | (0.83, 1.33) | 0.01 | (-0.02, 0.03) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6125 |
| <130 | 1684 | 211 | 12.5 | 1687 | 240 | 14.2 | 0.1510 | 1.13 | ( 0.95, 1.35) | 1.16 | (0.95, 1.41) | 0.02 | (-0.01, 0.04) | |
| >=130 | 1591 | 137 | 8.6 | 1643 | 149 | 9.1 | 0.6344 | 1.06 | ( 0.85, 1.32) | 1.06 | (0.83, 1.35) | 0.00 | (-0.01, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2713 |
| <75 | 1653 | 206 | 12.5 | 1612 | 222 | 13.8 | 0.2652 | 1.11 | ( 0.93, 1.32) | 1.12 | (0.92, 1.38) | 0.01 | (-0.01, 0.04) | |
| 75 to <85 | 1005 | 97 | 9.7 | 1085 | 102 | 9.4 | 0.8479 | 0.97 | ( 0.75, 1.27) | 0.97 | (0.73, 1.30) | 0.00 | (-0.03, 0.02) | |
| >=85 | 617 | 45 | 7.3 | 633 | 65 | 10.3 | 0.0613 | 1.41 | ( 0.98, 2.03) | 1.46 | (0.98, 2.17) | 0.03 | ( 0.00, 0.06) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0077 |
| <30 | 250 | 32 | 12.8 | 263 | 38 | 14.4 | 0.5885 | 1.13 | ( 0.73, 1.73) | 1.15 | (0.69, 1.90) | 0.02 | (-0.04, 0.08) | |
| 30 to <45 | 898 | 130 | 14.5 | 909 | 106 | 11.7 | 0.0754 | 0.81 | ( 0.63, 1.02) | 0.78 | (0.59, 1.03) | -0.03 | (-0.06, 0.00) | |
| >=45 | 2126 | 186 | 8.7 | 2158 | 245 | 11.4 | 0.0046 | 1.30 | ( 1.08, 1.56) | 1.34 | (1.09, 1.63) | 0.03 | ( 0.01, 0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2695 |
| Normal (<30) | 1216 | 145 | 11.9 | 1243 | 167 | 13.4 | 0.2629 | 1.13 | ( 0.91, 1.39) | 1.15 | (0.90, 1.45) | 0.02 | (-0.01, 0.04) | |
| Microalbuminuria (30 to <=300) | 1548 | 157 | 10.1 | 1546 | 183 | 11.8 | 0.1299 | 1.17 | ( 0.96, 1.43) | 1.19 | (0.95, 1.49) | 0.02 | ( 0.00, 0.04) | |
| Macroalbuminuria (>300) | 500 | 45 | 9.0 | 525 | 38 | 7.2 | 0.2963 | 0.80 | ( 0.53, 1.21) | 0.79 | (0.50, 1.23) | -0.02 | (-0.05, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2089 |
| Low, moderate or high | 2430 | 241 | 9.9 | 2495 | 288 | 11.5 | 0.0664 | 1.16 | ( 0.99, 1.37) | 1.18 | (0.99, 1.42) | 0.02 | ( 0.00, 0.03) | |
| Very high | 834 | 106 | 12.7 | 820 | 100 | 12.2 | 0.7441 | 0.96 | ( 0.74, 1.24) | 0.95 | (0.71, 1.27) | -0.01 | (-0.04, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6813 |
| No | 572 | 65 | 11.4 | 578 | 68 | 11.8 | 0.8365 | 1.03 | ( 0.75, 1.42) | 1.04 | (0.72, 1.49) | 0.00 | (-0.03, 0.04) | |
| Yes | 2703 | 283 | 10.5 | 2752 | 321 | 11.7 | 0.1611 | 1.11 | ( 0.96, 1.30) | 1.13 | (0.95, 1.34) | 0.01 | ( 0.00, 0.03) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8013 |
| No | 344 | 33 | 9.6 | 349 | 39 | 11.2 | 0.5091 | 1.16 | ( 0.75, 1.79) | 1.18 | (0.72, 1.92) | 0.02 | (-0.03, 0.06) | |
| Yes | 2931 | 315 | 10.7 | 2981 | 350 | 11.7 | 0.2284 | 1.09 | ( 0.95, 1.26) | 1.10 | (0.94, 1.30) | 0.01 | (-0.01, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | 0.8617 |
| No | 275 | 17 | 6.2 | 307 | 20 | 6.5 | 0.8903 | 1.04 | ( 0.56, 1.95) | 1.05 | (0.54, 2.04) | 0.00 (-0.04, 0.04) | |
| Yes | 3000 | 331 | 11.0 | 3023 | 369 | 12.2 | 0.1571 | 1.11 | ( 0.96, 1.27) | 1.12 | (0.96, 1.31) | 0.01 ( 0.00, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 549 | 16.8 | 3330 | 521 | 15.6 | 0.2088 | 0.93 | ( 0.84, 1.04) | 0.92 | (0.81, 1.05) | -0.01 | (-0.03, 0.01) | |
| Study | | | | | | | | | | | | | | 0.7673 |
| 1245.110 | 2001 | 365 | 18.2 | 2052 | 353 | 17.2 | 0.3868 | 0.94 | ( 0.83, 1.08) | 0.93 | (0.79, 1.09) | -0.01 | (-0.03, 0.01) | |
| 1245.121 | 1274 | 184 | 14.4 | 1278 | 168 | 13.1 | 0.3421 | 0.91 | ( 0.75, 1.11) | 0.90 | (0.72, 1.12) | -0.01 | (-0.04, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.7155 |
| Male | 2023 | 328 | 16.2 | 2068 | 318 | 15.4 | 0.4579 | 0.95 | ( 0.82, 1.09) | 0.94 | (0.79, 1.11) | -0.01 | (-0.03, 0.01) | |
| Female | 1252 | 221 | 17.7 | 1262 | 203 | 16.1 | 0.2827 | 0.91 | ( 0.76, 1.08) | 0.89 | (0.72, 1.10) | -0.02 | (-0.05, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.8762 |
| <65 | 766 | 132 | 17.2 | 705 | 112 | 15.9 | 0.4707 | 0.92 | ( 0.73, 1.16) | 0.90 | (0.69, 1.19) | -0.01 | (-0.05, 0.02) | |
| >=65 | 2509 | 417 | 16.6 | 2625 | 409 | 15.6 | 0.3164 | 0.94 | ( 0.83, 1.06) | 0.93 | (0.80, 1.08) | -0.01 | (-0.03, 0.01) | |
| Region | | | | | | | | | | | | | | 0.9990 |
| North America | 434 | 95 | 21.9 | 432 | 89 | 20.6 | 0.6362 | 0.94 | ( 0.73, 1.21) | 0.92 | (0.67, 1.28) | -0.01 | (-0.07, 0.04) | |
| Latin America | 931 | 152 | 16.3 | 944 | 145 | 15.4 | 0.5938 | 0.94 | ( 0.77, 1.16) | 0.93 | (0.73, 1.20) | -0.01 | (-0.04, 0.02) | |
| Europe | 1334 | 212 | 15.9 | 1361 | 199 | 14.6 | 0.3551 | 0.92 | ( 0.77, 1.10) | 0.91 | (0.73, 1.12) | -0.01 | (-0.04, 0.01) | |
| Asia | 405 | 54 | 13.3 | 413 | 53 | 12.8 | 0.8153 | 0.96 | ( 0.67, 1.37) | 0.95 | (0.63, 1.43) | -0.01 | (-0.05, 0.04) | |
| Other | 171 | 36 | 21.1 | 180 | 35 | 19.4 | 0.6231 | 0.90 | ( 0.60, 1.36) | 0.88 | (0.52, 1.49) | -0.02 | (-0.10, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0826 |
| Diabetic | 1739 | 311 | 17.9 | 1779 | 322 | 18.1 | 0.8941 | 1.01 | ( 0.88, 1.16) | 1.01 | (0.85, 1.20) | 0.00 | (-0.02, 0.03) | |
| Non-Diabetic | 1536 | 238 | 15.5 | 1551 | 199 | 12.8 | 0.0335 | 0.83 | ( 0.70, 0.99) | 0.80 | (0.65, 0.98) | -0.03 | (-0.05, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5410 |
| <30 | 1975 | 304 | 15.4 | 1930 | 268 | 13.9 | 0.1635 | 0.90 | ( 0.77, 1.04) | 0.88 | (0.74, 1.05) | -0.02 | (-0.04, 0.01) | |
| >=30 | 1300 | 245 | 18.8 | 1400 | 253 | 18.1 | 0.6273 | 0.96 | ( 0.82, 1.13) | 0.95 | (0.78, 1.16) | -0.01 | (-0.04, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3850 |
| <130 | 1684 | 276 | 16.4 | 1687 | 246 | 14.6 | 0.1358 | 0.89 | ( 0.76, 1.04) | 0.87 | (0.72, 1.05) | -0.02 | (-0.04, 0.01) | |
| >=130 | 1591 | 273 | 17.2 | 1643 | 275 | 16.7 | 0.7693 | 0.98 | ( 0.84, 1.14) | 0.97 | (0.81, 1.17) | 0.00 | (-0.03, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2063 |
| <75 | 1653 | 286 | 17.3 | 1612 | 282 | 17.5 | 0.9166 | 1.01 | ( 0.87, 1.17) | 1.01 | (0.84, 1.21) | 0.00 | (-0.02, 0.03) | |
| 75 to <85 | 1005 | 175 | 17.4 | 1085 | 152 | 14.0 | 0.0336 | 0.81 | ( 0.66, 0.98) | 0.77 | (0.61, 0.98) | -0.03 | (-0.06, 0.00) | |
| >=85 | 617 | 88 | 14.3 | 633 | 87 | 13.7 | 0.8014 | 0.97 | ( 0.73, 1.27) | 0.96 | (0.70, 1.32) | 0.00 | (-0.04, 0.03) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9013 |
| <30 | 250 | 77 | 30.8 | 263 | 73 | 27.8 | 0.6022 | 0.93 | ( 0.71, 1.22) | 0.90 | (0.61, 1.33) | -0.02 | (-0.10, 0.06) | |
| 30 to <45 | 898 | 190 | 21.2 | 909 | 186 | 20.5 | 0.6966 | 0.96 | ( 0.81, 1.15) | 0.96 | (0.76, 1.20) | -0.01 | (-0.04, 0.03) | |
| >=45 | 2126 | 282 | 13.3 | 2158 | 262 | 12.1 | 0.2559 | 0.91 | ( 0.78, 1.07) | 0.90 | (0.75, 1.08) | -0.01 | (-0.03, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.7968 |
| Normal (<30) | 1216 | 189 | 15.5 | 1243 | 175 | 14.1 | 0.3017 | 0.90 | ( 0.75, 1.09) | 0.89 | (0.71, 1.11) | -0.01 | (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 240 | 15.5 | 1546 | 235 | 15.2 | 0.7963 | 0.98 | ( 0.83, 1.15) | 0.97 | (0.80, 1.19) | 0.00 | (-0.03, 0.02) | |
| Macroalbuminuria (>300) | 500 | 117 | 23.4 | 525 | 111 | 21.1 | 0.4185 | 0.91 | ( 0.72, 1.14) | 0.88 | (0.66, 1.19) | -0.02 | (-0.07, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2988 |
| Low, moderate or high | 2430 | 339 | 14.0 | 2495 | 315 | 12.6 | 0.1614 | 0.90 | ( 0.78, 1.04) | 0.89 | (0.75, 1.05) | -0.01 | (-0.03, 0.01) | |
| Very high | 834 | 208 | 24.9 | 820 | 206 | 25.1 | 0.8674 | 1.01 | ( 0.86, 1.20) | 1.02 | (0.81, 1.27) | 0.00 | (-0.04, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7192 |
| No | 572 | 101 | 17.7 | 578 | 91 | 15.7 | 0.3894 | 0.89 | ( 0.69, 1.16) | 0.87 | (0.64, 1.19) | -0.02 | (-0.06, 0.02) | |
| Yes | 2703 | 448 | 16.6 | 2752 | 430 | 15.6 | 0.3216 | 0.94 | ( 0.83, 1.06) | 0.93 | (0.80, 1.07) | -0.01 | (-0.03, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8475 |
| No | 344 | 66 | 19.2 | 349 | 60 | 17.2 | 0.5399 | 0.91 | ( 0.66, 1.24) | 0.89 | (0.60, 1.30) | -0.02 | (-0.08, 0.04) | |
| Yes | 2931 | 483 | 16.5 | 2981 | 461 | 15.5 | 0.2719 | 0.94 | ( 0.83, 1.05) | 0.92 | (0.80, 1.06) | -0.01 | (-0.03, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4712 |
| No | 275 | 38 | 13.8 | 307 | 34 | 11.1 | 0.3153 | 0.80 | ( 0.52, 1.24) | 0.78 | (0.47, 1.27) | -0.03 | (-0.08, 0.03) | |
| Yes | 3000 | 511 | 17.0 | 3023 | 487 | 16.1 | 0.3214 | 0.94 | ( 0.84, 1.06) | 0.93 | (0.81, 1.07) | -0.01 | (-0.03, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 130 | 4.0 | 3330 | 95 | 2.9 | 0.0123 | 0.72 | ( 0.55, 0.93) | 0.71 | (0.54, 0.93) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.3366 |
| 1245.110 | 2001 | 84 | 4.2 | 2052 | 56 | 2.7 | 0.0105 | 0.65 | ( 0.47, 0.91) | 0.64 | (0.45, 0.90) | -0.01 | (-0.03, 0.00) | |
| 1245.121 | 1274 | 46 | 3.6 | 1278 | 39 | 3.1 | 0.4314 | 0.85 | ( 0.56, 1.29) | 0.84 | (0.54, 1.30) | -0.01 | (-0.02, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0013 |
| Male | 2023 | 84 | 4.2 | 2068 | 80 | 3.9 | 0.6434 | 0.93 | ( 0.69, 1.26) | 0.93 | (0.68, 1.27) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 46 | 3.7 | 1262 | 15 | 1.2 | <0.0001 | 0.32 | ( 0.18, 0.57) | 0.31 | (0.17, 0.56) | -0.03 | (-0.04,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.8819 |
| <65 | 766 | 29 | 3.8 | 705 | 20 | 2.8 | 0.3017 | 0.74 | ( 0.42, 1.31) | 0.74 | (0.41, 1.32) | -0.01 | (-0.03, 0.01) | |
| >=65 | 2509 | 101 | 4.0 | 2625 | 75 | 2.9 | 0.0214 | 0.71 | ( 0.53, 0.95) | 0.70 | (0.52, 0.95) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | 0.6833 |
| North America | 434 | 32 | 7.4 | 432 | 26 | 6.0 | 0.4238 | 0.82 | ( 0.49, 1.35) | 0.80 | (0.47, 1.37) | -0.01 | (-0.05, 0.02) | |
| Latin America | 931 | 16 | 1.7 | 944 | 9 | 1.0 | 0.1562 | 0.56 | ( 0.25, 1.26) | 0.56 | (0.24, 1.27) | -0.01 | (-0.02, 0.00) | |
| Europe | 1334 | 44 | 3.3 | 1361 | 38 | 2.8 | 0.4582 | 0.85 | ( 0.56, 1.30) | 0.85 | (0.54, 1.32) | 0.00 | (-0.02, 0.01) | |
| Asia | 405 | 21 | 5.2 | 413 | 13 | 3.1 | 0.1592 | 0.61 | ( 0.31, 1.22) | 0.60 | (0.30, 1.22) | -0.02 | (-0.05, 0.01) | |
| Other | 171 | 17 | 9.9 | 180 | 9 | 5.0 | 0.0657 | 0.50 | ( 0.24, 1.06) | 0.47 | (0.21, 1.07) | -0.05 | (-0.11, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9763 |
| Diabetic | 1739 | 65 | 3.7 | 1779 | 48 | 2.7 | 0.0803 | 0.72 | ( 0.50, 1.04) | 0.71 | (0.49, 1.04) | -0.01 | (-0.02, 0.00) | |
| Non-Diabetic | 1536 | 65 | 4.2 | 1551 | 47 | 3.0 | 0.0742 | 0.72 | ( 0.50, 1.04) | 0.71 | (0.48, 1.04) | -0.01 | (-0.03, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7028 |
| <30 | 1975 | 84 | 4.3 | 1930 | 57 | 3.0 | 0.0303 | 0.70 | ( 0.50, 0.97) | 0.69 | (0.49, 0.97) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1300 | 46 | 3.5 | 1400 | 38 | 2.7 | 0.2308 | 0.77 | ( 0.51, 1.18) | 0.77 | (0.50, 1.19) | -0.01 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7995 |
| <130 | 1684 | 74 | 4.4 | 1687 | 55 | 3.3 | 0.0844 | 0.74 | ( 0.53, 1.04) | 0.73 | (0.51, 1.04) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1591 | 56 | 3.5 | 1643 | 40 | 2.4 | 0.0697 | 0.69 | ( 0.46, 1.03) | 0.68 | (0.45, 1.03) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2853 |
| <75 | 1653 | 74 | 4.5 | 1612 | 62 | 3.8 | 0.3711 | 0.86 | ( 0.62, 1.20) | 0.85 | (0.61, 1.21) | -0.01 | (-0.02, 0.01) | |
| 75 to <85 | 1005 | 34 | 3.4 | 1085 | 20 | 1.8 | 0.0277 | 0.55 | ( 0.32, 0.94) | 0.54 | (0.31, 0.94) | -0.02 | (-0.03, 0.00) | |
| >=85 | 617 | 22 | 3.6 | 633 | 13 | 2.1 | 0.1028 | 0.57 | ( 0.29, 1.13) | 0.56 | (0.28, 1.13) | -0.02 | (-0.03, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0804 |
| <30 | 250 | 12 | 4.8 | 263 | 19 | 7.2 | 0.2320 | 1.55 | ( 0.75, 3.22) | 1.59 | (0.75, 3.39) | 0.03 | (-0.02, 0.07) | |
| 30 to <45 | 898 | 53 | 5.9 | 909 | 33 | 3.6 | 0.0236 | 0.62 | ( 0.40, 0.94) | 0.60 | (0.39, 0.94) | -0.02 | (-0.04, 0.00) | |
| >=45 | 2126 | 65 | 3.1 | 2158 | 43 | 2.0 | 0.0257 | 0.65 | ( 0.44, 0.95) | 0.64 | (0.44, 0.95) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1646 |
| Normal (<30) | 1216 | 57 | 4.7 | 1243 | 35 | 2.8 | 0.0145 | 0.60 | ( 0.40, 0.91) | 0.59 | (0.38, 0.90) | -0.02 | (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 60 | 3.9 | 1546 | 42 | 2.7 | 0.0708 | 0.70 | ( 0.48, 1.03) | 0.69 | (0.46, 1.03) | -0.01 | (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 500 | 13 | 2.6 | 525 | 18 | 3.4 | 0.4393 | 1.32 | ( 0.65, 2.66) | 1.33 | (0.64, 2.74) | 0.01 | (-0.01, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0765 |
| Low, moderate or high | 2430 | 86 | 3.5 | 2495 | 53 | 2.1 | 0.0027 | 0.60 | ( 0.43, 0.84) | 0.59 | (0.42, 0.84) | -0.01 | (-0.02, 0.00) | |
| Very high | 834 | 44 | 5.3 | 820 | 42 | 5.1 | 0.8890 | 0.97 | ( 0.64, 1.47) | 0.97 | (0.63, 1.50) | 0.00 | (-0.02, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.8316 |
| No | 572 | 36 | 6.3 | 578 | 25 | 4.3 | 0.1363 | 0.69 | ( 0.42, 1.13) | 0.67 | (0.40, 1.14) | -0.02 | (-0.05, 0.01) | |
| Yes | 2703 | 94 | 3.5 | 2752 | 70 | 2.5 | 0.0435 | 0.73 | ( 0.54, 0.99) | 0.72 | (0.53, 0.99) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7743 |
| No | 344 | 11 | 3.2 | 349 | 7 | 2.0 | 0.3291 | 0.63 | ( 0.25, 1.60) | 0.62 | (0.24, 1.62) | -0.01 | (-0.04, 0.01) | |
| Yes | 2931 | 119 | 4.1 | 2981 | 88 | 3.0 | 0.0203 | 0.73 | ( 0.55, 0.95) | 0.72 | (0.54, 0.95) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.7166 |
| No | 275 | 5 | 1.8 | 307 | 3 | 1.0 | 0.3978 | 0.57 | ( 0.15, 2.14) | 0.56 | (0.15, 2.17) | -0.01 | (-0.03, 0.01) | |
| Yes | 3000 | 125 | 4.2 | 3023 | 92 | 3.0 | 0.0192 | 0.73 | ( 0.56, 0.95) | 0.72 | (0.55, 0.95) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 30 | 0.9 | 3330 | 32 | 1.0 | 0.8575 | 1.05 | ( 0.64, 1.72) | 1.05 | (0.63, 1.73) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.3318 |
| 1245.110 | 2001 | 20 | 1.0 | 2052 | 25 | 1.2 | 0.5063 | 1.22 | ( 0.68, 2.19) | 1.22 | (0.68, 2.21) | 0.00 | ( 0.00, 0.01) | |
| 1245.121 | 1274 | 10 | 0.8 | 1278 | 7 | 0.5 | 0.4615 | 0.70 | ( 0.27, 1.83) | 0.70 | (0.26, 1.83) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.1513 |
| Male | 2023 | 23 | 1.1 | 2068 | 19 | 0.9 | 0.4869 | 0.81 | ( 0.44, 1.48) | 0.81 | (0.44, 1.48) | 0.00 | (-0.01, 0.00) | |
| Female | 1252 | 7 | 0.6 | 1262 | 13 | 1.0 | 0.2003 | 1.77 | ( 0.73, 4.30) | 1.78 | (0.73, 4.36) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3871 |
| <65 | 766 | 8 | 1.0 | 705 | 5 | 0.7 | 0.4916 | 0.68 | ( 0.22, 2.06) | 0.68 | (0.22, 2.08) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 22 | 0.9 | 2625 | 27 | 1.0 | 0.5717 | 1.18 | ( 0.67, 2.06) | 1.18 | (0.67, 2.07) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.8768 |
| North America | 434 | 6 | 1.4 | 432 | 9 | 2.1 | 0.4303 | 1.51 | ( 0.54, 4.20) | 1.52 | (0.54, 4.30) | 0.01 | (-0.01, 0.02) | |
| Latin America | 931 | 9 | 1.0 | 944 | 8 | 0.8 | 0.8012 | 0.89 | ( 0.34, 2.29) | 0.88 | (0.34, 2.30) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 5 | 0.4 | 1361 | 7 | 0.5 | 0.5946 | 1.36 | ( 0.43, 4.29) | 1.37 | (0.43, 4.32) | 0.00 | ( 0.00, 0.01) | |
| Asia | 405 | 6 | 1.5 | 413 | 5 | 1.2 | 0.7320 | 0.82 | ( 0.26, 2.57) | 0.82 | (0.26, 2.58) | 0.00 | (-0.02, 0.01) | |
| Other | 171 | 4 | 2.3 | 180 | 3 | 1.7 | 0.6826 | 0.75 | ( 0.18, 3.04) | 0.74 | (0.18, 3.07) | -0.01 | (-0.04, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6444 |
| Diabetic | 1739 | 29 | 1.7 | 1779 | 30 | 1.7 | 0.9749 | 1.01 | ( 0.61, 1.67) | 1.01 | (0.60, 1.69) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 1536 | 1 | 0.1 | 1551 | 2 | 0.1 | 0.6252 | 1.65 | ( 0.22,12.47) | 1.65 | (0.22,12.50) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7125 |
| <30 | 1975 | 17 | 0.9 | 1930 | 19 | 1.0 | 0.6983 | 1.14 | ( 0.59, 2.19) | 1.14 | (0.59, 2.20) | 0.00 | ( 0.00, 0.01) | |
| >=30 | 1300 | 13 | 1.0 | 1400 | 13 | 0.9 | 0.8776 | 0.94 | ( 0.44, 2.03) | 0.94 | (0.43, 2.04) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4870 |
| <130 | 1684 | 14 | 0.8 | 1687 | 12 | 0.7 | 0.6734 | 0.85 | ( 0.39, 1.83) | 0.85 | (0.39, 1.84) | 0.00 | (-0.01, 0.00) | |
| >=130 | 1591 | 16 | 1.0 | 1643 | 20 | 1.2 | 0.5627 | 1.21 | ( 0.63, 2.33) | 1.22 | (0.63, 2.35) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5516 |
| <75 | 1653 | 15 | 0.9 | 1612 | 14 | 0.9 | 0.8873 | 0.95 | ( 0.46, 1.96) | 0.95 | (0.46, 1.97) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 9 | 0.9 | 1085 | 14 | 1.3 | 0.3845 | 1.44 | ( 0.63, 3.32) | 1.45 | (0.62, 3.36) | 0.00 | ( 0.00, 0.01) | |
| >=85 | 617 | 6 | 1.0 | 633 | 4 | 0.6 | 0.5009 | 0.65 | ( 0.18, 2.29) | 0.65 | (0.18, 2.31) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0606 |
| <30 | 250 | 3 | 1.2 | 263 | 9 | 3.4 | 0.0889 | 2.76 | ( 0.81, 9.35) | 2.84 | (0.82, 9.87) | 0.02 | ( 0.00, 0.05) | |
| 30 to <45 | 898 | 7 | 0.8 | 909 | 11 | 1.2 | 0.3588 | 1.55 | ( 0.60, 4.00) | 1.56 | (0.60, 4.04) | 0.00 | ( 0.00, 0.01) | |
| >=45 | 2126 | 20 | 0.9 | 2158 | 12 | 0.6 | 0.1387 | 0.59 | ( 0.29, 1.20) | 0.58 | (0.28, 1.20) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9403 |
| Normal (<30) | 1216 | 6 | 0.5 | 1243 | 6 | 0.5 | 0.9637 | 0.97 | ( 0.32, 3.01) | 0.97 | (0.31, 3.03) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 13 | 0.8 | 1546 | 15 | 1.0 | 0.7195 | 1.15 | ( 0.55, 2.40) | 1.15 | (0.54, 2.42) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 500 | 11 | 2.2 | 525 | 11 | 2.1 | 0.9050 | 0.95 | ( 0.42, 2.17) | 0.95 | (0.41, 2.21) | 0.00 | (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2556 |
| Low, moderate or high | 2430 | 17 | 0.7 | 2495 | 14 | 0.6 | 0.5328 | 0.80 | ( 0.39, 1.62) | 0.80 | (0.39, 1.62) | 0.00 | (-0.01, 0.00) | |
| Very high | 834 | 13 | 1.6 | 820 | 18 | 2.2 | 0.3220 | 1.43 | ( 0.70, 2.89) | 1.44 | (0.70, 2.95) | 0.01 | (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6709 |
| No | 572 | 8 | 1.4 | 578 | 10 | 1.7 | 0.6465 | 1.24 | ( 0.49, 3.11) | 1.24 | (0.49, 3.17) | 0.00 | (-0.01, 0.02) | |
| Yes | 2703 | 22 | 0.8 | 2752 | 22 | 0.8 | 0.9419 | 0.98 | ( 0.54, 1.76) | 0.98 | (0.54, 1.77) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6130 |
| No | 344 | 4 | 1.2 | 349 | 3 | 0.9 | 0.6758 | 0.75 | ( 0.19, 2.93) | 0.75 | (0.19, 3.00) | 0.00 | (-0.02, 0.01) | |
| Yes | 2931 | 26 | 0.9 | 2981 | 29 | 1.0 | 0.7454 | 1.09 | ( 0.64, 1.85) | 1.09 | (0.64, 1.86) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5446 |
| No | 275 | 5 | 1.8 | 307 | 4 | 1.3 | 0.6187 | 0.73 | ( 0.21, 2.50) | 0.73 | (0.21, 2.55) | -0.01 | (-0.03, 0.02) | |
| Yes | 3000 | 25 | 0.8 | 3023 | 28 | 0.9 | 0.7059 | 1.11 | ( 0.65, 1.90) | 1.11 | (0.65, 1.91) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 317 | 9.7 | 3330 | 262 | 7.9 | 0.0091 | 0.81 | ( 0.69, 0.95) | 0.80 | (0.67, 0.95) | -0.02 | (-0.03, 0.00) | |
| Study | | | | | | | | | | | | | | 0.5211 |
| 1245.110 | 2001 | 195 | 9.7 | 2052 | 169 | 8.2 | 0.0930 | 0.85 | ( 0.69, 1.03) | 0.83 | (0.67, 1.03) | -0.02 | (-0.03, 0.00) | |
| 1245.121 | 1274 | 122 | 9.6 | 1278 | 93 | 7.3 | 0.0366 | 0.76 | ( 0.59, 0.98) | 0.74 | (0.56, 0.98) | -0.02 | (-0.04, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.1780 |
| Male | 2023 | 193 | 9.5 | 2068 | 174 | 8.4 | 0.2065 | 0.88 | ( 0.73, 1.07) | 0.87 | (0.70, 1.08) | -0.01 | (-0.03, 0.01) | |
| Female | 1252 | 124 | 9.9 | 1262 | 88 | 7.0 | 0.0083 | 0.70 | ( 0.54, 0.92) | 0.68 | (0.51, 0.91) | -0.03 | (-0.05,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.9006 |
| <65 | 766 | 77 | 10.1 | 705 | 59 | 8.4 | 0.2494 | 0.83 | ( 0.60, 1.14) | 0.81 | (0.57, 1.16) | -0.02 | (-0.05, 0.01) | |
| >=65 | 2509 | 240 | 9.6 | 2625 | 203 | 7.7 | 0.0193 | 0.81 | ( 0.68, 0.97) | 0.79 | (0.65, 0.96) | -0.02 | (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | | 0.1708 |
| North America | 434 | 33 | 7.6 | 432 | 44 | 10.2 | 0.1832 | 1.34 | ( 0.87, 2.06) | 1.38 | (0.86, 2.21) | 0.03 | (-0.01, 0.06) | |
| Latin America | 931 | 105 | 11.3 | 944 | 79 | 8.4 | 0.0368 | 0.75 | ( 0.56, 0.98) | 0.72 | (0.53, 0.98) | -0.03 | (-0.06, 0.00) | |
| Europe | 1334 | 111 | 8.3 | 1361 | 87 | 6.4 | 0.0562 | 0.77 | ( 0.59, 1.01) | 0.75 | (0.56, 1.01) | -0.02 | (-0.04, 0.00) | |
| Asia | 405 | 45 | 11.1 | 413 | 31 | 7.5 | 0.0766 | 0.68 | ( 0.44, 1.05) | 0.65 | (0.40, 1.05) | -0.04 | (-0.08, 0.00) | |
| Other | 171 | 23 | 13.5 | 180 | 21 | 11.7 | 0.6133 | 0.87 | ( 0.50, 1.51) | 0.85 | (0.45, 1.60) | -0.02 | (-0.09, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4583 |
| Diabetic | 1739 | 204 | 11.7 | 1779 | 162 | 9.1 | 0.0104 | 0.78 | ( 0.64, 0.94) | 0.75 | (0.61, 0.94) | -0.03 | (-0.05,-0.01) | |
| Non-Diabetic | 1536 | 113 | 7.4 | 1551 | 100 | 6.4 | 0.3206 | 0.88 | ( 0.68, 1.14) | 0.87 | (0.66, 1.15) | -0.01 | (-0.03, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6786 |
| <30 | 1975 | 195 | 9.9 | 1930 | 151 | 7.8 | 0.0239 | 0.79 | ( 0.65, 0.97) | 0.77 | (0.62, 0.97) | -0.02 | (-0.04, 0.00) | |
| >=30 | 1300 | 122 | 9.4 | 1400 | 111 | 7.9 | 0.1848 | 0.85 | ( 0.66, 1.08) | 0.83 | (0.64, 1.09) | -0.01 | (-0.04, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5092 |
| <130 | 1684 | 157 | 9.3 | 1687 | 121 | 7.2 | 0.0216 | 0.77 | ( 0.61, 0.96) | 0.75 | (0.58, 0.96) | -0.02 | (-0.04, 0.00) | |
| >=130 | 1591 | 160 | 10.1 | 1643 | 141 | 8.6 | 0.1455 | 0.85 | ( 0.69, 1.06) | 0.84 | (0.66, 1.06) | -0.01 | (-0.03, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2536 |
| <75 | 1653 | 174 | 10.5 | 1612 | 152 | 9.4 | 0.2911 | 0.89 | ( 0.73, 1.10) | 0.88 | (0.70, 1.11) | -0.01 | (-0.03, 0.01) | |
| 75 to <85 | 1005 | 93 | 9.3 | 1085 | 66 | 6.1 | 0.0065 | 0.66 | ( 0.49, 0.89) | 0.64 | (0.46, 0.88) | -0.03 | (-0.05,-0.01) | |
| >=85 | 617 | 50 | 8.1 | 633 | 44 | 7.0 | 0.4359 | 0.86 | ( 0.58, 1.26) | 0.85 | (0.55, 1.29) | -0.01 | (-0.04, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7563 |
| <30 | 250 | 38 | 15.2 | 263 | 33 | 12.5 | 0.3747 | 0.82 | ( 0.53, 1.27) | 0.80 | (0.48, 1.32) | -0.03 | (-0.09, 0.03) | |
| 30 to <45 | 898 | 121 | 13.5 | 909 | 92 | 10.1 | 0.0268 | 0.75 | ( 0.58, 0.97) | 0.72 | (0.54, 0.96) | -0.03 | (-0.06, 0.00) | |
| >=45 | 2126 | 158 | 7.4 | 2158 | 137 | 6.3 | 0.1582 | 0.85 | ( 0.68, 1.06) | 0.84 | (0.67, 1.07) | -0.01 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4670 |
| Normal (<30) | 1216 | 123 | 10.1 | 1243 | 90 | 7.2 | 0.0114 | 0.72 | ( 0.55, 0.93) | 0.69 | (0.52, 0.92) | -0.03 | (-0.05,-0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 130 | 8.4 | 1546 | 116 | 7.5 | 0.3551 | 0.89 | ( 0.70, 1.14) | 0.88 | (0.68, 1.15) | -0.01 | (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 500 | 63 | 12.6 | 525 | 55 | 10.5 | 0.3013 | 0.84 | ( 0.60, 1.17) | 0.82 | (0.56, 1.20) | -0.02 | (-0.06, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9577 |
| Low, moderate or high | 2430 | 194 | 8.0 | 2495 | 162 | 6.5 | 0.0426 | 0.81 | ( 0.66, 0.99) | 0.80 | (0.64, 0.99) | -0.01 | (-0.03, 0.00) | |
| Very high | 834 | 123 | 14.7 | 820 | 99 | 12.1 | 0.1125 | 0.82 | ( 0.64, 1.05) | 0.79 | (0.60, 1.06) | -0.03 | (-0.06, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.8115 |
| No | 572 | 46 | 8.0 | 578 | 36 | 6.2 | 0.2329 | 0.77 | ( 0.51, 1.18) | 0.76 | (0.48, 1.19) | -0.02 | (-0.05, 0.01) | |
| Yes | 2703 | 271 | 10.0 | 2752 | 226 | 8.2 | 0.0195 | 0.82 | ( 0.69, 0.97) | 0.80 | (0.67, 0.97) | -0.02 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7706 |
| No | 344 | 35 | 10.2 | 349 | 27 | 7.7 | 0.2613 | 0.76 | ( 0.47, 1.23) | 0.74 | (0.44, 1.25) | -0.02 | (-0.07, 0.02) | |
| Yes | 2931 | 282 | 9.6 | 2981 | 235 | 7.9 | 0.0177 | 0.82 | ( 0.69, 0.97) | 0.80 | (0.67, 0.96) | -0.02 | (-0.03, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 1 Proportion of patients with adverse events of special interest and other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.0756 |
| No | 275 | 19 | 6.9 | 307 | 28 | 9.1 | 0.3275 | 1.32 ( 0.76, 2.31) | 1.35 (0.74, 2.48) | 0.02 (-0.02, 0.07) | |
| Yes | 3000 | 298 | 9.9 | 3023 | 234 | 7.7 | 0.0027 | 0.78 ( 0.66, 0.92) | 0.76 (0.64, 0.91) | -0.02 (-0.04,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 31 | 0.9 | 3330 | 25 | 0.8 | 0.3859 | 0.79 | (0.47, 1.34) | 0.79 | (0.47, 1.34) | 0.00 | (-0.01, 0.00) | |
| Study | | | | | | | | | | | | | | 0.0757 |
| 1245.110 | 2001 | 22 | 1.1 | 2052 | 12 | 0.6 | 0.0725 | 0.53 | (0.26, 1.07) | 0.53 | (0.26, 1.07) | -0.01 | (-0.01, 0.00) | |
| 1245.121 | 1274 | 9 | 0.7 | 1278 | 13 | 1.0 | 0.3959 | 1.44 | (0.62, 3.36) | 1.44 | (0.62, 3.39) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.1418 |
| Male | 2023 | 22 | 1.1 | 2068 | 22 | 1.1 | 0.9396 | 0.98 | (0.54, 1.76) | 0.98 | (0.54, 1.77) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 9 | 0.7 | 1262 | 3 | 0.2 | 0.0836 | 0.34 | (0.09, 1.23) | 0.33 | (0.09, 1.23) | 0.00 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.2411 |
| <65 | 766 | 11 | 1.4 | 705 | 12 | 1.7 | 0.6957 | 1.18 | (0.52, 2.64) | 1.18 | (0.52, 2.69) | 0.00 | (-0.01, 0.02) | |
| >=65 | 2509 | 20 | 0.8 | 2625 | 13 | 0.5 | 0.1754 | 0.62 | (0.31, 1.25) | 0.62 | (0.31, 1.25) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.9798 |
| North America | 434 | 6 | 1.4 | 432 | 5 | 1.2 | 0.7645 | 0.84 | (0.26, 2.71) | 0.83 | (0.25, 2.75) | 0.00 | (-0.02, 0.01) | |
| Latin America | 931 | 8 | 0.9 | 944 | 8 | 0.8 | 0.9678 | 0.98 | (0.37, 2.62) | 0.98 | (0.37, 2.63) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 14 | 1.0 | 1361 | 11 | 0.8 | 0.5170 | 0.77 | (0.35, 1.69) | 0.77 | (0.35, 1.70) | 0.00 | (-0.01, 0.00) | |
| Asia | 405 | 1 | 0.2 | 413 | 0 | 0 | 0.5461 | 0.49 | (0.05, 5.26) | 0.49 | (0.04, 5.34) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 2 | 1.2 | 180 | 1 | 0.6 | 0.6036 | 0.59 | (0.08, 4.48) | 0.58 | (0.08, 4.51) | -0.01 | (-0.03, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8376 |
| Diabetic | 1739 | 28 | 1.6 | 1779 | 23 | 1.3 | 0.4311 | 0.80 | (0.46, 1.39) | 0.80 | (0.46, 1.39) | 0.00 | (-0.01, 0.00) | |
| Non-Diabetic | 1536 | 3 | 0.2 | 1551 | 2 | 0.1 | 0.6470 | 0.66 | (0.11, 3.94) | 0.66 | (0.11, 3.95) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7277 |
| <30 | 1975 | 13 | 0.7 | 1930 | 11 | 0.6 | 0.7263 | 0.87 | (0.39, 1.92) | 0.87 | (0.39, 1.93) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1300 | 18 | 1.4 | 1400 | 14 | 1.0 | 0.3511 | 0.72 | (0.36, 1.44) | 0.72 | (0.35, 1.45) | 0.00 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8275 |
| <130 | 1684 | 13 | 0.8 | 1687 | 11 | 0.7 | 0.6787 | 0.85 | (0.38, 1.88) | 0.84 | (0.38, 1.89) | 0.00 | (-0.01, 0.00) | |
| >=130 | 1591 | 18 | 1.1 | 1643 | 14 | 0.9 | 0.4194 | 0.75 | (0.37, 1.51) | 0.75 | (0.37, 1.51) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8699 |
| <75 | 1653 | 16 | 1.0 | 1612 | 14 | 0.9 | 0.7587 | 0.89 | (0.44, 1.82) | 0.89 | (0.44, 1.83) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 10 | 1.0 | 1085 | 7 | 0.6 | 0.3754 | 0.65 | (0.25, 1.70) | 0.65 | (0.25, 1.71) | 0.00 | (-0.01, 0.00) | |
| >=85 | 617 | 5 | 0.8 | 633 | 4 | 0.6 | 0.6970 | 0.77 | (0.21, 2.85) | 0.77 | (0.21, 2.88) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5290 |
| <30 | 250 | 2 | 0.8 | 263 | 4 | 1.5 | 0.4556 | 1.79 | (0.38, 8.42) | 1.80 | (0.38, 8.63) | 0.01 | (-0.01, 0.03) | |
| 30 to <45 | 898 | 8 | 0.9 | 909 | 5 | 0.6 | 0.3967 | 0.62 | (0.20, 1.89) | 0.62 | (0.20, 1.90) | 0.00 | (-0.01, 0.00) | |
| >=45 | 2126 | 21 | 1.0 | 2158 | 16 | 0.7 | 0.3829 | 0.75 | (0.39, 1.43) | 0.75 | (0.39, 1.44) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8712 |
| Normal (<30) | 1216 | 6 | 0.5 | 1243 | 6 | 0.5 | 0.9710 | 0.98 | (0.32, 3.03) | 0.98 | (0.32, 3.04) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 11 | 0.7 | 1546 | 9 | 0.6 | 0.6599 | 0.82 | (0.34, 1.97) | 0.82 | (0.34, 1.98) | 0.00 | (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 500 | 14 | 2.8 | 525 | 10 | 1.9 | 0.3484 | 0.68 | (0.30, 1.53) | 0.68 | (0.30, 1.54) | -0.01 | (-0.03, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8417 |
| Low, moderate or high | 2430 | 20 | 0.8 | 2495 | 17 | 0.7 | 0.5670 | 0.83 | (0.44, 1.58) | 0.83 | (0.43, 1.58) | 0.00 | (-0.01, 0.00) | |
| Very high | 834 | 11 | 1.3 | 820 | 8 | 1.0 | 0.5146 | 0.74 | (0.30, 1.83) | 0.74 | (0.30, 1.84) | 0.00 | (-0.01, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6106 |
| No | 572 | 4 | 0.7 | 578 | 2 | 0.3 | 0.4354 | 0.55 | (0.12, 2.54) | 0.55 | (0.12, 2.56) | 0.00 | (-0.01, 0.01) | |
| Yes | 2703 | 27 | 1.0 | 2752 | 23 | 0.8 | 0.5268 | 0.84 | (0.48, 1.45) | 0.84 | (0.48, 1.46) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2347 |
| No | 344 | 6 | 1.7 | 349 | 2 | 0.6 | 0.1456 | 0.32 | (0.06, 1.61) | 0.32 | (0.06, 1.60) | -0.01 | (-0.03, 0.00) | |
| Yes | 2931 | 25 | 0.9 | 2981 | 23 | 0.8 | 0.7281 | 0.90 | (0.52, 1.59) | 0.90 | (0.51, 1.60) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1421 |
| No | 275 | 4 | 1.5 | 307 | 0 | 0 | 0.0717 | 0.17 | (0.02, 1.50) | 0.17 | (0.02, 1.49) | -0.02 | (-0.03, 0.00) | |
| Yes | 3000 | 27 | 0.9 | 3023 | 25 | 0.8 | 0.7593 | 0.92 | (0.53, 1.58) | 0.92 | (0.53, 1.59) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 57 | 1.7 | 3330 | 38 | 1.1 | 0.0402 | 0.65 | (0.44, 0.98) | 0.65 | (0.43, 0.98) | -0.01 | (-0.01, 0.00) | |
| Study | | | | | | | | | | | | | | 0.7493 |
| 1245.110 | 2001 | 39 | 1.9 | 2052 | 25 | 1.2 | 0.0621 | 0.63 | (0.38, 1.03) | 0.62 | (0.37, 1.03) | -0.01 | (-0.02, 0.00) | |
| 1245.121 | 1274 | 18 | 1.4 | 1278 | 13 | 1.0 | 0.3617 | 0.72 | (0.35, 1.46) | 0.72 | (0.35, 1.47) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0193 |
| Male | 2023 | 31 | 1.5 | 2068 | 30 | 1.5 | 0.8277 | 0.95 | (0.57, 1.56) | 0.95 | (0.57, 1.57) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 26 | 2.1 | 1262 | 8 | 0.6 | 0.0020 | 0.32 | (0.15, 0.68) | 0.31 | (0.14, 0.68) | -0.01 | (-0.02,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.9376 |
| <65 | 766 | 8 | 1.0 | 705 | 5 | 0.7 | 0.4873 | 0.68 | (0.22, 2.06) | 0.67 | (0.22, 2.07) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 49 | 2.0 | 2625 | 33 | 1.3 | 0.0471 | 0.64 | (0.42,<1.00) | 0.64 | (0.41, 1.00) | -0.01 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.3959 |
| North America | 434 | 10 | 2.3 | 432 | 8 | 1.9 | 0.6381 | 0.80 | (0.32, 2.01) | 0.80 | (0.31, 2.04) | 0.00 | (-0.02, 0.01) | |
| Latin America | 931 | 9 | 1.0 | 944 | 11 | 1.2 | 0.6649 | 1.21 | (0.51, 2.91) | 1.22 | (0.50, 2.94) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 23 | 1.7 | 1361 | 9 | 0.7 | 0.0107 | 0.38 | (0.18, 0.82) | 0.38 | (0.18, 0.82) | -0.01 | (-0.02, 0.00) | |
| Asia | 405 | 14 | 3.5 | 413 | 9 | 2.2 | 0.2778 | 0.63 | (0.28, 1.45) | 0.63 | (0.27, 1.47) | -0.01 | (-0.04, 0.01) | |
| Other | 171 | 1 | 0.6 | 180 | 1 | 0.6 | 0.9704 | 0.96 | (0.10, 9.11) | 0.96 | (0.10, 9.30) | 0.00 | (-0.02, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5774 |
| Diabetic | 1739 | 28 | 1.6 | 1779 | 21 | 1.2 | 0.2740 | 0.73 | (0.42, 1.28) | 0.73 | (0.41, 1.29) | 0.00 | (-0.01, 0.00) | |
| Non-Diabetic | 1536 | 29 | 1.9 | 1551 | 17 | 1.1 | 0.0691 | 0.58 | (0.32, 1.05) | 0.58 | (0.31, 1.05) | -0.01 | (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1604 |
| <30 | 1975 | 47 | 2.4 | 1930 | 26 | 1.3 | 0.0161 | 0.56 | (0.35, 0.90) | 0.56 | (0.34, 0.90) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1300 | 10 | 0.8 | 1400 | 12 | 0.9 | 0.7864 | 1.12 | (0.48, 2.60) | 1.12 | (0.48, 2.62) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9590 |
| <130 | 1684 | 36 | 2.1 | 1687 | 24 | 1.4 | 0.1102 | 0.66 | (0.40, 1.10) | 0.66 | (0.39, 1.10) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1591 | 21 | 1.3 | 1643 | 14 | 0.9 | 0.2004 | 0.65 | (0.33, 1.27) | 0.64 | (0.33, 1.27) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8600 |
| <75 | 1653 | 37 | 2.2 | 1612 | 26 | 1.6 | 0.1855 | 0.72 | (0.44, 1.18) | 0.71 | (0.43, 1.18) | -0.01 | (-0.02, 0.00) | |
| 75 to <85 | 1005 | 12 | 1.2 | 1085 | 7 | 0.6 | 0.1864 | 0.54 | (0.21, 1.37) | 0.54 | (0.21, 1.37) | -0.01 | (-0.01, 0.00) | |
| >=85 | 617 | 8 | 1.3 | 633 | 5 | 0.8 | 0.3787 | 0.61 | (0.20, 1.86) | 0.61 | (0.20, 1.87) | -0.01 | (-0.02, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5528 |
| <30 | 250 | 7 | 2.8 | 263 | 6 | 2.3 | 0.7866 | 0.86 | (0.30, 2.50) | 0.86 | (0.29, 2.58) | 0.00 | (-0.03, 0.02) | |
| 30 to <45 | 898 | 11 | 1.2 | 909 | 10 | 1.1 | 0.8015 | 0.90 | (0.38, 2.10) | 0.90 | (0.38, 2.11) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 39 | 1.8 | 2158 | 22 | 1.0 | 0.0237 | 0.55 | (0.33, 0.93) | 0.55 | (0.32, 0.93) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1482 |
| Normal (<30) | 1216 | 23 | 1.9 | 1243 | 10 | 0.8 | 0.0190 | 0.43 | (0.20, 0.89) | 0.42 | (0.20, 0.89) | -0.01 | (-0.02, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 32 | 2.1 | 1546 | 23 | 1.5 | 0.2177 | 0.72 | (0.42, 1.22) | 0.71 | (0.42, 1.22) | -0.01 | (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 500 | 2 | 0.4 | 525 | 5 | 1.0 | 0.2852 | 2.37 | (0.46,12.13) | 2.38 | (0.46,12.33) | 0.01 | ( 0.00, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2880 |
| Low, moderate or high | 2430 | 44 | 1.8 | 2495 | 26 | 1.0 | 0.0220 | 0.57 | (0.35, 0.93) | 0.57 | (0.35, 0.93) | -0.01 | (-0.01, 0.00) | |
| Very high | 834 | 13 | 1.6 | 820 | 12 | 1.5 | 0.8842 | 0.94 | (0.43, 2.06) | 0.94 | (0.43, 2.08) | 0.00 | (-0.01, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3510 |
| No | 572 | 17 | 3.0 | 578 | 8 | 1.4 | 0.0658 | 0.47 | (0.20, 1.07) | 0.46 | (0.20, 1.07) | -0.02 | (-0.03, 0.00) | |
| Yes | 2703 | 40 | 1.5 | 2752 | 30 | 1.1 | 0.1985 | 0.74 | (0.46, 1.18) | 0.73 | (0.45, 1.18) | 0.00 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4017 |
| No | 344 | 13 | 3.8 | 349 | 6 | 1.7 | 0.0959 | 0.45 | (0.18, 1.18) | 0.45 | (0.17, 1.18) | -0.02 | (-0.05, 0.00) | |
| Yes | 2931 | 44 | 1.5 | 2981 | 32 | 1.1 | 0.1420 | 0.71 | (0.45, 1.12) | 0.71 | (0.45, 1.12) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1469 |
| No | 275 | 5 | 1.8 | 307 | 0 | 0 | 0.0389 | 0.15 | (0.02, 1.22) | 0.14 | (0.02, 1.21) | -0.02 | (-0.04, 0.00) | |
| Yes | 3000 | 52 | 1.7 | 3023 | 38 | 1.3 | 0.1257 | 0.72 | (0.48, 1.10) | 0.72 | (0.47, 1.10) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 6 | 0.2 | 3330 | 6 | 0.2 | 0.9686 | 0.98 | (0.33, 2.90) | 0.98 | (0.33, 2.91) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.4696 |
| 1245.110 | 2001 | 5 | 0.2 | 2052 | 6 | 0.3 | 0.7948 | 1.17 | (0.36, 3.83) | 1.17 | (0.36, 3.84) | 0.00 | ( 0.00, 0.00) | |
| 1245.121 | 1274 | 1 | 0.1 | 1278 | 0 | 0 | 0.4780 | 0.33 | (0.01, 8.15) | 0.33 | (0.01, 8.16) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | |
| Male | 2023 | 3 | 0.1 | 2068 | 3 | 0.1 | | | | | | | | |
| Female | 1252 | 3 | 0.2 | 1262 | 3 | 0.2 | | | | | | | | |
| Age [years] | | | | | | | | | | | | | | |
| <65 | 766 | 6 | 0.8 | 705 | 1 | 0.1 | | | | | | | | |
| >=65 | 2509 | 0 | 0 | 2625 | 5 | 0.2 | | | | | | | | |
| Region | | | | | | | | | | | | | | |
| North America | 434 | 2 | 0.5 | 432 | 3 | 0.7 | | | | | | | | |
| Latin America | 931 | 1 | 0.1 | 944 | 0 | 0 | | | | | | | | |
| Europe | 1334 | 0 | 0 | 1361 | 1 | 0.1 | | | | | | | | |
| Asia | 405 | 1 | 0.2 | 413 | 0 | 0 | | | | | | | | |
| Other | 171 | 2 | 1.2 | 180 | 2 | 1.1 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9885 |
| Diabetic | 1739 | 6 | 0.3 | 1779 | 6 | 0.3 | 0.9574 | 0.97 | (0.33, 2.88) | 0.97 | (0.33, 2.89) | 0.00 | ( 0.00, 0.00) | |
| Non-Diabetic | 1536 | 0 | 0 | 1551 | 0 | 0 | 0.9956 | 0.99 | (0.06,15.85) | 0.99 | (0.06,15.88) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | |
| <30 | 1975 | 3 | 0.2 | 1930 | 2 | 0.1 | | | | | | | | |
| >=30 | 1300 | 3 | 0.2 | 1400 | 4 | 0.3 | | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | |
| <130 | 1684 | 2 | 0.1 | 1687 | 1 | 0.1 | | | | | | | | |
| >=130 | 1591 | 4 | 0.3 | 1643 | 5 | 0.3 | | | | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 1653 | 1 | 0.1 | 1612 | 3 | 0.2 | | | | | | |
| 75 to <85 | 1005 | 3 | 0.3 | 1085 | 3 | 0.3 | | | | | | |
| >=85 | 617 | 2 | 0.3 | 633 | 0 | 0 | | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 250 | 2 | 0.8 | 263 | 1 | 0.4 | | | | | | |
| 30 to <45 | 898 | 1 | 0.1 | 909 | 2 | 0.2 | | | | | | |
| >=45 | 2126 | 3 | 0.1 | 2158 | 3 | 0.1 | | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 1216 | 1 | 0.1 | 1243 | 1 | 0.1 | | | | | | |
| Microalbuminuria (30 to <=300) | 1548 | 3 | 0.2 | 1546 | 2 | 0.1 | | | | | | |
| Macroalbuminuria (>300) | 500 | 2 | 0.4 | 525 | 3 | 0.6 | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | |
| Low, moderate or high | 2430 | 4 | 0.2 | 2495 | 4 | 0.2 | | | | | | |
| Very high | 834 | 2 | 0.2 | 820 | 2 | 0.2 | | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | |
| No | 572 | 2 | 0.3 | 578 | 1 | 0.2 | | | | | | |
| Yes | 2703 | 4 | 0.1 | 2752 | 5 | 0.2 | | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.2596 |
| No | 344 | 0 | 0 | 349 | 2 | 0.6 | 0.3278 | 2.89 | (0.31,26.81) | 2.91 (0.31,27.66) | 0.01 (-0.01, 0.02) | |
| Yes | 2931 | 6 | 0.2 | 2981 | 4 | 0.1 | 0.5185 | 0.67 | (0.20, 2.24) | 0.67 (0.20, 2.25) | 0.00 ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 275 | 1 | 0.4 | 307 | 2 | 0.7 | | | | | |
| Yes | 3000 | 5 | 0.2 | 3023 | 4 | 0.1 | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 18 | 0.5 | 3330 | 21 | 0.6 | 0.6676 | 1.15 | (0.61, 2.15) | 1.15 | (0.61, 2.16) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.9861 |
| 1245.110 | 2001 | 11 | 0.5 | 2052 | 13 | 0.6 | 0.7281 | 1.15 | (0.52, 2.57) | 1.15 | (0.52, 2.58) | 0.00 | ( 0.00, 0.01) | |
| 1245.121 | 1274 | 7 | 0.5 | 1278 | 8 | 0.6 | 0.8004 | 1.14 | (0.41, 3.13) | 1.14 | (0.41, 3.15) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0279 |
| Male | 2023 | 15 | 0.7 | 2068 | 10 | 0.5 | 0.2901 | 0.65 | (0.29, 1.45) | 0.65 | (0.29, 1.45) | 0.00 | (-0.01, 0.00) | |
| Female | 1252 | 3 | 0.2 | 1262 | 11 | 0.9 | 0.0396 | 3.25 | (0.99,10.71) | 3.27 | (0.99,10.84) | 0.01 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3008 |
| <65 | 766 | 3 | 0.4 | 705 | 6 | 0.9 | 0.2595 | 2.18 | (0.54, 8.69) | 2.19 | (0.54, 8.78) | 0.00 | ( 0.00, 0.01) | |
| >=65 | 2509 | 15 | 0.6 | 2625 | 15 | 0.6 | 0.9013 | 0.96 | (0.47, 1.95) | 0.96 | (0.47, 1.96) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | 0.3234 |
| North America | 434 | 3 | 0.7 | 432 | 8 | 1.9 | 0.1272 | 2.68 | (0.72,10.06) | 2.72 | (0.71,10.32) | 0.01 | ( 0.00, 0.03) | |
| Latin America | 931 | 5 | 0.5 | 944 | 6 | 0.6 | 0.7867 | 1.18 | (0.36, 3.87) | 1.18 | (0.36, 3.89) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 8 | 0.6 | 1361 | 3 | 0.2 | 0.1216 | 0.37 | (0.10, 1.38) | 0.37 | (0.10, 1.38) | 0.00 | (-0.01, 0.00) | |
| Asia | 405 | 0 | 0 | 413 | 1 | 0.2 | 0.5806 | 1.95 | (0.17,21.82) | 1.96 | (0.18,21.85) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 2 | 1.2 | 180 | 3 | 1.7 | 0.7202 | 1.35 | (0.26, 6.95) | 1.35 | (0.26, 7.04) | 0.00 | (-0.02, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9237 |
| Diabetic | 1739 | 18 | 1.0 | 1779 | 21 | 1.2 | 0.6814 | 1.14 | (0.61, 2.13) | 1.14 | (0.61, 2.15) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 1536 | 0 | 0 | 1551 | 0 | 0 | 0.9956 | 0.99 | (0.06,15.85) | 0.99 | (0.06,15.88) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9160 |
| <30 | 1975 | 7 | 0.4 | 1930 | 8 | 0.4 | 0.7455 | 1.18 | (0.43, 3.27) | 1.18 | (0.43, 3.28) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1300 | 11 | 0.8 | 1400 | 13 | 0.9 | 0.8098 | 1.10 | (0.50, 2.46) | 1.10 | (0.49, 2.48) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4558 |
| <130 | 1684 | 10 | 0.6 | 1687 | 9 | 0.5 | 0.8071 | 0.89 | (0.36, 2.20) | 0.89 | (0.36, 2.21) | 0.00 | (-0.01, 0.00) | |
| >=130 | 1591 | 8 | 0.5 | 1643 | 12 | 0.7 | 0.4138 | 1.45 | (0.59, 3.54) | 1.45 | (0.59, 3.56) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2661 |
| <75 | 1653 | 13 | 0.8 | 1612 | 9 | 0.6 | 0.4278 | 0.71 | (0.30, 1.66) | 0.71 | (0.30, 1.66) | 0.00 | (-0.01, 0.00) | |
| 75 to <85 | 1005 | 5 | 0.5 | 1085 | 10 | 0.9 | 0.2496 | 1.86 | (0.64, 5.42) | 1.87 | (0.64, 5.48) | 0.00 | ( 0.00, 0.01) | |
| >=85 | 617 | 0 | 0 | 633 | 2 | 0.3 | 0.3319 | 2.91 | (0.30,27.88) | 2.92 | (0.30,28.15) | 0.00 | ( 0.00, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1227 |
| <30 | 250 | 1 | 0.4 | 263 | 5 | 1.9 | 0.1484 | 3.49 | (0.57,21.32) | 3.54 | (0.57,21.93) | 0.01 | ( 0.00, 0.03) | |
| 30 to <45 | 898 | 5 | 0.6 | 909 | 9 | 1.0 | 0.2925 | 1.78 | (0.60, 5.31) | 1.79 | (0.60, 5.37) | 0.00 | ( 0.00, 0.01) | |
| >=45 | 2126 | 12 | 0.6 | 2158 | 7 | 0.3 | 0.2362 | 0.57 | (0.23, 1.45) | 0.57 | (0.23, 1.46) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5705 |
| Normal (<30) | 1216 | 5 | 0.4 | 1243 | 3 | 0.2 | 0.4621 | 0.59 | (0.14, 2.45) | 0.59 | (0.14, 2.46) | 0.00 | (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 8 | 0.5 | 1546 | 10 | 0.6 | 0.6394 | 1.25 | (0.49, 3.17) | 1.25 | (0.49, 3.18) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 500 | 5 | 1.0 | 525 | 8 | 1.5 | 0.4540 | 1.53 | (0.50, 4.67) | 1.53 | (0.50, 4.73) | 0.01 | (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1342 |
| Low, moderate or high | 2430 | 11 | 0.5 | 2495 | 8 | 0.3 | 0.4648 | 0.71 | (0.29, 1.77) | 0.71 | (0.29, 1.78) | 0.00 | ( 0.00, 0.00) | |
| Very high | 834 | 7 | 0.8 | 820 | 13 | 1.6 | 0.1578 | 1.91 | (0.77, 4.78) | 1.93 | (0.76, 4.87) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2116 |
| No | 572 | 2 | 0.3 | 578 | 6 | 1.0 | 0.1847 | 2.58 | (0.60,11.05) | 2.60 | (0.60,11.24) | 0.01 | ( 0.00, 0.02) | |
| Yes | 2703 | 16 | 0.6 | 2752 | 15 | 0.5 | 0.8212 | 0.92 | (0.46, 1.86) | 0.92 | (0.45, 1.87) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2431 |
| No | 344 | 3 | 0.9 | 349 | 1 | 0.3 | 0.3215 | 0.40 | (0.06, 2.61) | 0.40 | (0.06, 2.66) | -0.01 | (-0.02, 0.01) | |
| Yes | 2931 | 15 | 0.5 | 2981 | 20 | 0.7 | 0.4276 | 1.31 | (0.67, 2.55) | 1.31 | (0.67, 2.57) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8129 |
| No | 275 | 1 | 0.4 | 307 | 1 | 0.3 | 0.9113 | 0.88 | (0.09, 8.39) | 0.88 | (0.09, 8.51) | 0.00 | (-0.01, 0.01) | |
| Yes | 3000 | 17 | 0.6 | 3023 | 20 | 0.7 | 0.6374 | 1.17 | (0.61, 2.22) | 1.17 | (0.61, 2.24) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 65 | 2.0 | 3330 | 79 | 2.4 | 0.2871 | 1.19 | (0.86, 1.65) | 1.20 | (0.86, 1.67) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.5008 |
| 1245.110 | 2001 | 45 | 2.2 | 2052 | 59 | 2.9 | 0.2074 | 1.28 | (0.87, 1.88) | 1.29 | (0.87, 1.91) | 0.01 | ( 0.00, 0.02) | |
| 1245.121 | 1274 | 20 | 1.6 | 1278 | 20 | 1.6 | 0.9920 | 1.00 | (0.54, 1.84) | 1.00 | (0.53, 1.86) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0056 |
| Male | 2023 | 42 | 2.1 | 2068 | 33 | 1.6 | 0.2501 | 0.77 | (0.49, 1.21) | 0.76 | (0.48, 1.21) | 0.00 | (-0.01, 0.00) | |
| Female | 1252 | 23 | 1.8 | 1262 | 46 | 3.6 | 0.0057 | 1.98 | (1.21, 3.24) | 2.02 | (1.21, 3.35) | 0.02 | ( 0.01, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.9638 |
| <65 | 766 | 9 | 1.2 | 705 | 10 | 1.4 | 0.6824 | 1.21 | (0.49, 2.96) | 1.21 | (0.49, 3.00) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 56 | 2.2 | 2625 | 69 | 2.6 | 0.3526 | 1.18 | (0.83, 1.67) | 1.18 | (0.83, 1.69) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.8519 |
| North America | 434 | 14 | 3.2 | 432 | 14 | 3.2 | 0.9933 | 1.00 | (0.48, 2.08) | 1.00 | (0.47, 2.13) | 0.00 | (-0.02, 0.02) | |
| Latin America | 931 | 18 | 1.9 | 944 | 25 | 2.6 | 0.2841 | 1.38 | (0.76, 2.52) | 1.40 | (0.76, 2.58) | 0.01 | (-0.01, 0.02) | |
| Europe | 1334 | 25 | 1.9 | 1361 | 26 | 1.9 | 0.9485 | 1.02 | (0.59, 1.75) | 1.02 | (0.59, 1.77) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 4 | 1.0 | 413 | 7 | 1.7 | 0.3961 | 1.69 | (0.50, 5.70) | 1.70 | (0.49, 5.85) | 0.01 | (-0.01, 0.02) | |
| Other | 171 | 4 | 2.3 | 180 | 7 | 3.9 | 0.4196 | 1.64 | (0.49, 5.53) | 1.67 | (0.48, 5.82) | 0.02 | (-0.02, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7543 |
| Diabetic | 1739 | 36 | 2.1 | 1779 | 42 | 2.4 | 0.5677 | 1.14 | (0.73, 1.77) | 1.14 | (0.73, 1.79) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 1536 | 29 | 1.9 | 1551 | 37 | 2.4 | 0.3426 | 1.26 | (0.78, 2.04) | 1.27 | (0.78, 2.07) | 0.00 | (-0.01, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.0926 |
| <30 | 1975 | 40 | 2.0 | 1930 | 36 | 1.9 | 0.6949 | 0.91 | (0.59, 1.43) | 0.91 | (0.58, 1.44) | 0.00 | (-0.01, 0.01) | |
| >=30 | 1300 | 25 | 1.9 | 1400 | 43 | 3.1 | 0.0521 | 1.61 | (0.99, 2.62) | 1.63 | (0.99, 2.69) | 0.01 | ( 0.00, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3063 |
| <130 | 1684 | 31 | 1.8 | 1687 | 44 | 2.6 | 0.1427 | 1.40 | (0.89, 2.21) | 1.41 | (0.89, 2.25) | 0.01 | ( 0.00, 0.02) | |
| >=130 | 1591 | 34 | 2.1 | 1643 | 35 | 2.1 | 0.9942 | 1.00 | (0.63, 1.59) | 1.00 | (0.62, 1.61) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9878 |
| <75 | 1653 | 37 | 2.2 | 1612 | 43 | 2.7 | 0.4357 | 1.19 | (0.77, 1.84) | 1.19 | (0.76, 1.86) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 18 | 1.8 | 1085 | 23 | 2.1 | 0.5857 | 1.18 | (0.65, 2.16) | 1.19 | (0.64, 2.20) | 0.00 | (-0.01, 0.02) | |
| >=85 | 617 | 10 | 1.6 | 633 | 13 | 2.1 | 0.5600 | 1.27 | (0.56, 2.88) | 1.28 | (0.56, 2.94) | 0.00 | (-0.01, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8589 |
| <30 | 250 | 10 | 4.0 | 263 | 10 | 3.8 | 0.9064 | 0.95 | (0.39, 2.31) | 0.95 | (0.38, 2.34) | 0.00 | (-0.04, 0.03) | |
| 30 to <45 | 898 | 23 | 2.6 | 909 | 28 | 3.1 | 0.5194 | 1.20 | (0.69, 2.06) | 1.20 | (0.69, 2.11) | 0.01 | (-0.01, 0.02) | |
| >=45 | 2126 | 32 | 1.5 | 2158 | 41 | 1.9 | 0.3292 | 1.26 | (0.79, 1.99) | 1.26 | (0.79, 2.01) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5368 |
| Normal (<30) | 1216 | 20 | 1.6 | 1243 | 32 | 2.6 | 0.1113 | 1.56 | (0.90, 2.71) | 1.58 | (0.90, 2.77) | 0.01 | ( 0.00, 0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 34 | 2.2 | 1546 | 36 | 2.3 | 0.8183 | 1.06 | (0.66, 1.68) | 1.06 | (0.66, 1.70) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 500 | 10 | 2.0 | 525 | 11 | 2.1 | 0.8956 | 1.06 | (0.45, 2.46) | 1.06 | (0.45, 2.52) | 0.00 | (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.6599 |
| Low, moderate or high | 2430 | 39 | 1.6 | 2495 | 52 | 2.1 | 0.2212 | 1.29 | (0.86, 1.95) | 1.30 | (0.85, 1.97) | 0.00 | ( 0.00, 0.01) | |
| Very high | 834 | 25 | 3.0 | 820 | 27 | 3.3 | 0.7013 | 1.11 | (0.65, 1.90) | 1.11 | (0.64, 1.94) | 0.00 | (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.0654 |
| No | 572 | 12 | 2.1 | 578 | 25 | 4.3 | 0.0320 | 2.07 | (1.05, 4.08) | 2.12 | (1.05, 4.26) | 0.02 | ( 0.00, 0.04) | |
| Yes | 2703 | 53 | 2.0 | 2752 | 54 | 2.0 | 0.9859 | 1.00 | (0.68, 1.45) | 1.00 | (0.68, 1.46) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7923 |
| No | 344 | 11 | 3.2 | 349 | 12 | 3.4 | 0.8408 | 1.08 | (0.50, 2.37) | 1.09 | (0.48, 2.45) | 0.00 | (-0.02, 0.03) | |
| Yes | 2931 | 54 | 1.8 | 2981 | 67 | 2.2 | 0.2797 | 1.22 | (0.85, 1.73) | 1.22 | (0.85, 1.75) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8904 |
| No | 275 | 4 | 1.5 | 307 | 6 | 2.0 | 0.6709 | 1.29 | (0.40, 4.21) | 1.30 | (0.39, 4.34) | 0.00 | (-0.02, 0.03) | |
| Yes | 3000 | 61 | 2.0 | 3023 | 73 | 2.4 | 0.3227 | 1.18 | (0.85, 1.66) | 1.19 | (0.84, 1.68) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 10 | 0.3 | 3330 | 2 | 0.1 | 0.0190 | 0.20 | (0.04, 0.89) | 0.20 | (0.04, 0.89) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | |
| 1245.110 | 2001 | 8 | 0.4 | 2052 | 1 | <0.1 | | | | | | | | |
| 1245.121 | 1274 | 2 | 0.2 | 1278 | 1 | 0.1 | | | | | | | | |
| Sex | | | | | | | | | | | | | | 0.8190 |
| Male | 2023 | 8 | 0.4 | 2068 | 2 | 0.1 | 0.0526 | 0.24 | (0.05, 1.15) | 0.24 | (0.05, 1.15) | 0.00 | (-0.01, 0.00) | |
| Female | 1252 | 2 | 0.2 | 1262 | 0 | 0 | 0.3213 | 0.34 | (0.04, 3.23) | 0.34 | (0.03, 3.23) | 0.00 | ( 0.00, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.7681 |
| <65 | 766 | 2 | 0.3 | 705 | 0 | 0 | 0.3567 | 0.36 | (0.04, 3.46) | 0.36 | (0.04, 3.47) | 0.00 | (-0.01, 0.00) | |
| >=65 | 2509 | 8 | 0.3 | 2625 | 2 | 0.1 | 0.0491 | 0.24 | (0.05, 1.13) | 0.24 | (0.05, 1.13) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | |
| North America | 434 | 3 | 0.7 | 432 | 0 | 0 | | | | | | | | |
| Latin America | 931 | 2 | 0.2 | 944 | 0 | 0 | | | | | | | | |
| Europe | 1334 | 3 | 0.2 | 1361 | 2 | 0.1 | | | | | | | | |
| Asia | 405 | 2 | 0.5 | 413 | 0 | 0 | | | | | | | | |
| Other | 171 | 0 | 0 | 180 | 0 | 0 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | |
| Diabetic | 1739 | 6 | 0.3 | 1779 | 2 | 0.1 | | | | | | | | |
| Non-Diabetic | 1536 | 4 | 0.3 | 1551 | 0 | 0 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | |
| <30 | 1975 | 7 | 0.4 | 1930 | 2 | 0.1 | | | | | | | | |
| >=30 | 1300 | 3 | 0.2 | 1400 | 0 | 0 | | | | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | |
| <130 | 1684 | 7 | 0.4 | 1687 | 0 | 0 | | | | | | | | |
| >=130 | 1591 | 3 | 0.2 | 1643 | 2 | 0.1 | | | | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 1653 | 7 | 0.4 | 1612 | 1 | 0.1 | | | | | | |
| 75 to <85 | 1005 | 2 | 0.2 | 1085 | 1 | 0.1 | | | | | | |
| >=85 | 617 | 1 | 0.2 | 633 | 0 | 0 | | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 250 | 1 | 0.4 | 263 | 0 | 0 | | | | | | |
| 30 to <45 | 898 | 3 | 0.3 | 909 | 1 | 0.1 | | | | | | |
| >=45 | 2126 | 6 | 0.3 | 2158 | 1 | <0.1 | | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 1216 | 1 | 0.1 | 1243 | 1 | 0.1 | | | | | | |
| Microalbuminuria (30 to <=300) | 1548 | 6 | 0.4 | 1546 | 1 | 0.1 | | | | | | |
| Macroalbuminuria (>300) | 500 | 3 | 0.6 | 525 | 0 | 0 | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | |
| Low, moderate or high | 2430 | 7 | 0.3 | 2495 | 2 | 0.1 | | | | | | |
| Very high | 834 | 3 | 0.4 | 820 | 0 | 0 | | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | |
| No | 572 | 4 | 0.7 | 578 | 0 | 0 | | | | | | |
| Yes | 2703 | 6 | 0.2 | 2752 | 2 | 0.1 | | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6028 |
| No | 344 | 1 | 0.3 | 349 | 0 | 0 | 0.5093 | 0.46 (0.04, 4.89) | 0.46 (0.04, 5.01) | 0.00 (-0.01, 0.01) | | |
| Yes | 2931 | 9 | 0.3 | 2981 | 2 | 0.1 | 0.0312 | 0.22 (0.05,>1.00) | 0.22 (0.05, 1.00) | 0.00 ( 0.00, 0.00) | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3606 |
| No | 275 | 0 | 0 | 307 | 0 | 0 | 0.9161 | 0.86 | (0.05,13.65) | 0.86 | (0.05,13.88) | 0.00 | (-0.01, 0.01) | |
| Yes | 3000 | 10 | 0.3 | 3023 | 2 | 0.1 | 0.0198 | 0.20 | (0.04, 0.90) | 0.20 | (0.04, 0.90) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 22 | 0.7 | 3330 | 30 | 0.9 | 0.2977 | 1.34 | (0.77, 2.31) | 1.34 | (0.77, 2.33) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.5610 |
| 1245.110 | 2001 | 16 | 0.8 | 2052 | 24 | 1.2 | 0.2336 | 1.46 | (0.78, 2.75) | 1.47 | (0.78, 2.77) | 0.00 | ( 0.00, 0.01) | |
| 1245.121 | 1274 | 6 | 0.5 | 1278 | 6 | 0.5 | 0.9957 | 1.00 | (0.32, 3.08) | 1.00 | (0.32, 3.10) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0538 |
| Male | 2023 | 14 | 0.7 | 2068 | 11 | 0.5 | 0.5078 | 0.77 | (0.35, 1.69) | 0.77 | (0.35, 1.69) | 0.00 | (-0.01, 0.00) | |
| Female | 1252 | 8 | 0.6 | 1262 | 19 | 1.5 | 0.0355 | 2.35 | (1.03, 5.33) | 2.37 | (1.03, 5.43) | 0.01 | ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.4879 |
| <65 | 766 | 3 | 0.4 | 705 | 2 | 0.3 | 0.7240 | 0.73 | (0.12, 4.34) | 0.72 | (0.12, 4.36) | 0.00 | (-0.01, 0.00) | |
| >=65 | 2509 | 19 | 0.8 | 2625 | 28 | 1.1 | 0.2417 | 1.41 | (0.79, 2.52) | 1.42 | (0.79, 2.54) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.9280 |
| North America | 434 | 3 | 0.7 | 432 | 5 | 1.2 | 0.4751 | 1.67 | (0.40, 6.96) | 1.68 | (0.40, 7.08) | 0.00 | (-0.01, 0.02) | |
| Latin America | 931 | 5 | 0.5 | 944 | 7 | 0.7 | 0.5700 | 1.39 | (0.44, 4.36) | 1.39 | (0.44, 4.40) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 10 | 0.7 | 1361 | 11 | 0.8 | 0.8700 | 1.07 | (0.46, 2.52) | 1.07 | (0.45, 2.54) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 2 | 0.5 | 413 | 5 | 1.2 | 0.3130 | 2.14 | (0.47, 9.71) | 2.15 | (0.47, 9.74) | 0.01 | (-0.01, 0.02) | |
| Other | 171 | 2 | 1.2 | 180 | 2 | 1.1 | 0.9431 | 0.94 | (0.16, 5.34) | 0.94 | (0.16, 5.48) | 0.00 | (-0.03, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8406 |
| Diabetic | 1739 | 13 | 0.7 | 1779 | 17 | 1.0 | 0.5102 | 1.27 | (0.62, 2.62) | 1.28 | (0.62, 2.64) | 0.00 | ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 9 | 0.6 | 1551 | 13 | 0.8 | 0.4079 | 1.43 | (0.61, 3.33) | 1.43 | (0.61, 3.36) | 0.00 | ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1605 |
| <30 | 1975 | 15 | 0.8 | 1930 | 14 | 0.7 | 0.8718 | 0.94 | (0.46, 1.94) | 0.94 | (0.45, 1.96) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1300 | 7 | 0.5 | 1400 | 16 | 1.1 | 0.0842 | 2.13 | (0.88, 5.13) | 2.14 | (0.88, 5.20) | 0.01 | ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7632 |
| <130 | 1684 | 12 | 0.7 | 1687 | 15 | 0.9 | 0.5939 | 1.23 | (0.58, 2.61) | 1.23 | (0.57, 2.64) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 1591 | 10 | 0.6 | 1643 | 15 | 0.9 | 0.3545 | 1.45 | (0.66, 3.22) | 1.46 | (0.65, 3.25) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4956 |
| <75 | 1653 | 13 | 0.8 | 1612 | 12 | 0.7 | 0.8829 | 0.94 | (0.43, 2.06) | 0.94 | (0.43, 2.07) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 5 | 0.5 | 1085 | 11 | 1.0 | 0.1892 | 1.95 | (0.71, 5.36) | 1.96 | (0.71, 5.43) | 0.01 | ( 0.00, 0.01) | |
| >=85 | 617 | 4 | 0.6 | 633 | 7 | 1.1 | 0.4034 | 1.63 | (0.51, 5.21) | 1.64 | (0.51, 5.30) | 0.00 | (-0.01, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7383 |
| <30 | 250 | 4 | 1.6 | 263 | 5 | 1.9 | 0.7696 | 1.21 | (0.34, 4.29) | 1.21 | (0.34, 4.35) | 0.00 | (-0.02, 0.03) | |
| 30 to <45 | 898 | 10 | 1.1 | 909 | 11 | 1.2 | 0.8652 | 1.07 | (0.47, 2.47) | 1.08 | (0.46, 2.50) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 8 | 0.4 | 2158 | 14 | 0.6 | 0.2159 | 1.72 | (0.72, 4.09) | 1.72 | (0.72, 4.12) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9473 |
| Normal (<30) | 1216 | 7 | 0.6 | 1243 | 11 | 0.9 | 0.3741 | 1.53 | (0.60, 3.93) | 1.54 | (0.59, 3.98) | 0.00 | ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 10 | 0.6 | 1546 | 14 | 0.9 | 0.4152 | 1.40 | (0.62, 3.13) | 1.40 | (0.62, 3.16) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 500 | 4 | 0.8 | 525 | 5 | 1.0 | 0.7943 | 1.18 | (0.34, 4.05) | 1.18 | (0.34, 4.12) | 0.00 | (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5328 |
| Low, moderate or high | 2430 | 9 | 0.4 | 2495 | 16 | 0.6 | 0.1874 | 1.72 | (0.76, 3.88) | 1.72 | (0.76, 3.91) | 0.00 | ( 0.00, 0.01) | |
| Very high | 834 | 12 | 1.4 | 820 | 14 | 1.7 | 0.6322 | 1.20 | (0.56, 2.58) | 1.21 | (0.56, 2.63) | 0.00 | (-0.01, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1420 |
| No | 572 | 2 | 0.3 | 578 | 8 | 1.4 | 0.0707 | 3.38 | (0.83,13.77) | 3.42 | (0.83,14.06) | 0.01 | ( 0.00, 0.02) | |
| Yes | 2703 | 20 | 0.7 | 2752 | 22 | 0.8 | 0.8143 | 1.07 | (0.59, 1.97) | 1.08 | (0.59, 1.98) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5923 |
| No | 344 | 3 | 0.9 | 349 | 6 | 1.7 | 0.3520 | 1.81 | (0.51, 6.48) | 1.83 | (0.50, 6.68) | 0.01 | (-0.01, 0.03) | |
| Yes | 2931 | 19 | 0.6 | 2981 | 24 | 0.8 | 0.4895 | 1.23 | (0.68, 2.25) | 1.24 | (0.68, 2.26) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1687 |
| No | 275 | 3 | 1.1 | 307 | 1 | 0.3 | 0.2922 | 0.37 | (0.06, 2.50) | 0.37 | (0.05, 2.53) | -0.01 | (-0.02, 0.01) | |
| Yes | 3000 | 19 | 0.6 | 3023 | 29 | 1.0 | 0.1588 | 1.51 | (0.85, 2.68) | 1.51 | (0.85, 2.71) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 75 | 2.3 | 3330 | 85 | 2.6 | 0.4986 | 1.11 | (0.82, 1.51) | 1.11 | (0.81, 1.53) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.9587 |
| 1245.110 | 2001 | 55 | 2.7 | 2052 | 63 | 3.1 | 0.5427 | 1.12 | (0.78, 1.60) | 1.12 | (0.78, 1.62) | 0.00 | (-0.01, 0.01) | |
| 1245.121 | 1274 | 20 | 1.6 | 1278 | 22 | 1.7 | 0.7635 | 1.10 | (0.60, 2.00) | 1.10 | (0.60, 2.02) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.9800 |
| Male | 2023 | 35 | 1.7 | 2068 | 40 | 1.9 | 0.6284 | 1.12 | (0.71, 1.75) | 1.12 | (0.71, 1.77) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 40 | 3.2 | 1262 | 45 | 3.6 | 0.6297 | 1.11 | (0.73, 1.69) | 1.11 | (0.72, 1.72) | 0.00 | (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.2050 |
| <65 | 766 | 12 | 1.6 | 705 | 7 | 1.0 | 0.3202 | 0.63 | (0.25, 1.59) | 0.62 | (0.24, 1.59) | -0.01 | (-0.02, 0.01) | |
| >=65 | 2509 | 63 | 2.5 | 2625 | 78 | 3.0 | 0.3092 | 1.18 | (0.85, 1.64) | 1.19 | (0.85, 1.67) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.5803 |
| North America | 434 | 18 | 4.1 | 432 | 15 | 3.5 | 0.6004 | 0.84 | (0.43, 1.64) | 0.83 | (0.41, 1.67) | -0.01 | (-0.03, 0.02) | |
| Latin America | 931 | 13 | 1.4 | 944 | 11 | 1.2 | 0.6654 | 0.84 | (0.38, 1.86) | 0.84 | (0.37, 1.88) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 31 | 2.3 | 1361 | 35 | 2.6 | 0.6824 | 1.10 | (0.69, 1.78) | 1.11 | (0.68, 1.81) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 10 | 2.5 | 413 | 18 | 4.4 | 0.1580 | 1.71 | (0.80, 3.64) | 1.75 | (0.80, 3.85) | 0.02 | (-0.01, 0.04) | |
| Other | 171 | 3 | 1.8 | 180 | 6 | 3.3 | 0.4028 | 1.72 | (0.48, 6.20) | 1.75 | (0.47, 6.55) | 0.01 | (-0.02, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4380 |
| Diabetic | 1739 | 34 | 2.0 | 1779 | 44 | 2.5 | 0.3038 | 1.26 | (0.81, 1.96) | 1.27 | (0.81, 1.99) | 0.01 | ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 41 | 2.7 | 1551 | 41 | 2.6 | 0.9576 | 0.99 | (0.65, 1.51) | 0.99 | (0.64, 1.53) | 0.00 | (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8871 |
| <30 | 1975 | 49 | 2.5 | 1930 | 55 | 2.8 | 0.4996 | 1.14 | (0.78, 1.67) | 1.14 | (0.77, 1.69) | 0.00 | (-0.01, 0.01) | |
| >=30 | 1300 | 26 | 2.0 | 1400 | 30 | 2.1 | 0.7509 | 1.09 | (0.65, 1.83) | 1.09 | (0.64, 1.85) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7962 |
| <130 | 1684 | 35 | 2.1 | 1687 | 41 | 2.4 | 0.5170 | 1.16 | (0.74, 1.81) | 1.16 | (0.74, 1.84) | 0.00 | (-0.01, 0.01) | |
| >=130 | 1591 | 40 | 2.5 | 1643 | 44 | 2.7 | 0.7584 | 1.07 | (0.70, 1.63) | 1.07 | (0.69, 1.65) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8550 |
| <75 | 1653 | 45 | 2.7 | 1612 | 46 | 2.9 | 0.8428 | 1.04 | (0.69, 1.56) | 1.04 | (0.69, 1.58) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 19 | 1.9 | 1085 | 26 | 2.4 | 0.4171 | 1.27 | (0.71, 2.28) | 1.28 | (0.70, 2.33) | 0.01 | (-0.01, 0.02) | |
| >=85 | 617 | 11 | 1.8 | 633 | 13 | 2.1 | 0.7192 | 1.16 | (0.52, 2.57) | 1.16 | (0.52, 2.61) | 0.00 | (-0.01, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8098 |
| <30 | 250 | 6 | 2.4 | 263 | 9 | 3.4 | 0.4118 | 1.53 | (0.55, 4.23) | 1.55 | (0.54, 4.45) | 0.01 | (-0.02, 0.04) | |
| 30 to <45 | 898 | 28 | 3.1 | 909 | 30 | 3.3 | 0.8438 | 1.05 | (0.63, 1.75) | 1.05 | (0.62, 1.78) | 0.00 | (-0.01, 0.02) | |
| >=45 | 2126 | 41 | 1.9 | 2158 | 46 | 2.1 | 0.6533 | 1.10 | (0.73, 1.67) | 1.10 | (0.72, 1.69) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.0728 |
| Normal (<30) | 1216 | 32 | 2.6 | 1243 | 25 | 2.0 | 0.3019 | 0.76 | (0.45, 1.28) | 0.76 | (0.45, 1.29) | -0.01 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 29 | 1.9 | 1546 | 48 | 3.1 | 0.0302 | 1.64 | (1.04, 2.59) | 1.67 | (1.05, 2.66) | 0.01 | ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 500 | 13 | 2.6 | 525 | 12 | 2.3 | 0.7481 | 0.88 | (0.41, 1.91) | 0.88 | (0.40, 1.94) | 0.00 | (-0.02, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5834 |
| Low, moderate or high | 2430 | 49 | 2.0 | 2495 | 54 | 2.2 | 0.7362 | 1.07 | (0.73, 1.57) | 1.07 | (0.72, 1.58) | 0.00 | (-0.01, 0.01) | |
| Very high | 834 | 25 | 3.0 | 820 | 31 | 3.8 | 0.3505 | 1.28 | (0.76, 2.14) | 1.29 | (0.75, 2.21) | 0.01 | (-0.01, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3373 |
| No | 572 | 19 | 3.3 | 578 | 27 | 4.7 | 0.2357 | 1.41 | (0.80, 2.51) | 1.44 | (0.79, 2.62) | 0.01 | (-0.01, 0.04) | |
| Yes | 2703 | 56 | 2.1 | 2752 | 58 | 2.1 | 0.9427 | 1.01 | (0.70, 1.46) | 1.01 | (0.70, 1.47) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2297 |
| No | 344 | 14 | 4.1 | 349 | 10 | 2.9 | 0.3924 | 0.70 | (0.31, 1.58) | 0.70 | (0.30, 1.60) | -0.01 | (-0.04, 0.02) | |
| Yes | 2931 | 61 | 2.1 | 2981 | 75 | 2.5 | 0.2769 | 1.20 | (0.86, 1.68) | 1.21 | (0.86, 1.70) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.7080 |
| No | 275 | 6 | 2.2 | 307 | 9 | 2.9 | 0.5701 | 1.33 | (0.50, 3.55) | 1.34 | (0.49, 3.69) | 0.01 | (-0.02, 0.03) | |
| Yes | 3000 | 69 | 2.3 | 3023 | 76 | 2.5 | 0.5988 | 1.09 | (0.79, 1.50) | 1.09 | (0.79, 1.52) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 19 | 0.6 | 3330 | 23 | 0.7 | 0.5746 | 1.19 | (0.65, 2.18) | 1.19 | (0.65, 2.19) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.8000 |
| 1245.110 | 2001 | 13 | 0.6 | 2052 | 15 | 0.7 | 0.7547 | 1.13 | (0.54, 2.36) | 1.13 | (0.53, 2.37) | 0.00 | ( 0.00, 0.01) | |
| 1245.121 | 1274 | 6 | 0.5 | 1278 | 8 | 0.6 | 0.5961 | 1.33 | (0.46, 3.82) | 1.33 | (0.46, 3.85) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.7024 |
| Male | 2023 | 13 | 0.6 | 2068 | 17 | 0.8 | 0.5024 | 1.28 | (0.62, 2.62) | 1.28 | (0.62, 2.64) | 0.00 | ( 0.00, 0.01) | |
| Female | 1252 | 6 | 0.5 | 1262 | 6 | 0.5 | 0.9870 | 0.99 | (0.33, 2.95) | 0.99 | (0.33, 2.95) | 0.00 | (-0.01, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3518 |
| <65 | 766 | 4 | 0.5 | 705 | 2 | 0.3 | 0.5174 | 0.61 | (0.13, 2.81) | 0.60 | (0.13, 2.83) | 0.00 | (-0.01, 0.00) | |
| >=65 | 2509 | 15 | 0.6 | 2625 | 21 | 0.8 | 0.3843 | 1.34 | (0.69, 2.59) | 1.34 | (0.69, 2.61) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.8567 |
| North America | 434 | 4 | 0.9 | 432 | 3 | 0.7 | 0.7115 | 0.76 | (0.17, 3.35) | 0.75 | (0.17, 3.39) | 0.00 | (-0.01, 0.01) | |
| Latin America | 931 | 1 | 0.1 | 944 | 3 | 0.3 | 0.3768 | 2.31 | (0.34,15.66) | 2.32 | (0.34,15.75) | 0.00 | ( 0.00, 0.01) | |
| Europe | 1334 | 11 | 0.8 | 1361 | 11 | 0.8 | 0.9635 | 0.98 | (0.43, 2.25) | 0.98 | (0.42, 2.27) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 2 | 0.5 | 413 | 4 | 1.0 | 0.4767 | 1.73 | (0.37, 8.03) | 1.74 | (0.37, 8.20) | 0.00 | (-0.01, 0.02) | |
| Other | 171 | 1 | 0.6 | 180 | 2 | 1.1 | 0.6556 | 1.58 | (0.21,11.95) | 1.59 | (0.21,12.21) | 0.01 | (-0.02, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8669 |
| Diabetic | 1739 | 12 | 0.7 | 1779 | 14 | 0.8 | 0.7358 | 1.14 | (0.53, 2.46) | 1.14 | (0.53, 2.48) | 0.00 | ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 7 | 0.5 | 1551 | 9 | 0.6 | 0.6341 | 1.27 | (0.47, 3.40) | 1.27 | (0.47, 3.42) | 0.00 | ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5378 |
| <30 | 1975 | 11 | 0.6 | 1930 | 15 | 0.8 | 0.3956 | 1.40 | (0.64, 3.03) | 1.40 | (0.64, 3.06) | 0.00 | ( 0.00, 0.01) | |
| >=30 | 1300 | 8 | 0.6 | 1400 | 8 | 0.6 | 0.9083 | 0.94 | (0.36, 2.51) | 0.94 | (0.35, 2.52) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9431 |
| <130 | 1684 | 9 | 0.5 | 1687 | 11 | 0.7 | 0.6616 | 1.22 | (0.50, 2.94) | 1.22 | (0.50, 2.95) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 1591 | 10 | 0.6 | 1643 | 12 | 0.7 | 0.7219 | 1.16 | (0.50, 2.69) | 1.17 | (0.50, 2.71) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3437 |
| <75 | 1653 | 10 | 0.6 | 1612 | 14 | 0.9 | 0.3822 | 1.43 | (0.64, 3.21) | 1.43 | (0.64, 3.24) | 0.00 | ( 0.00, 0.01) | |
| 75 to <85 | 1005 | 4 | 0.4 | 1085 | 7 | 0.6 | 0.4335 | 1.62 | (0.48, 5.53) | 1.63 | (0.48, 5.58) | 0.00 | ( 0.00, 0.01) | |
| >=85 | 617 | 5 | 0.8 | 633 | 2 | 0.3 | 0.2709 | 0.44 | (0.10, 1.96) | 0.44 | (0.10, 1.97) | 0.00 | (-0.01, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9565 |
| <30 | 250 | 2 | 0.8 | 263 | 3 | 1.1 | 0.7064 | 1.35 | (0.29, 6.35) | 1.35 | (0.27, 6.68) | 0.00 | (-0.02, 0.02) | |
| 30 to <45 | 898 | 2 | 0.2 | 909 | 3 | 0.3 | 0.6953 | 1.38 | (0.27, 6.95) | 1.38 | (0.27, 7.01) | 0.00 | ( 0.00, 0.01) | |
| >=45 | 2126 | 15 | 0.7 | 2158 | 17 | 0.8 | 0.7562 | 1.12 | (0.56, 2.23) | 1.12 | (0.56, 2.24) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6366 |
| Normal (<30) | 1216 | 10 | 0.8 | 1243 | 9 | 0.7 | 0.7762 | 0.88 | (0.37, 2.11) | 0.88 | (0.36, 2.12) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 6 | 0.4 | 1546 | 10 | 0.6 | 0.3101 | 1.68 | (0.61, 4.63) | 1.68 | (0.61, 4.65) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 500 | 3 | 0.6 | 525 | 4 | 0.8 | 0.7660 | 1.25 | (0.28, 5.54) | 1.26 | (0.28, 5.63) | 0.00 | (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1946 |
| Low, moderate or high | 2430 | 17 | 0.7 | 2495 | 17 | 0.7 | 0.9307 | 0.97 | (0.50, 1.90) | 0.97 | (0.49, 1.90) | 0.00 | ( 0.00, 0.00) | |
| Very high | 834 | 2 | 0.2 | 820 | 6 | 0.7 | 0.1492 | 3.04 | (0.62,14.96) | 3.06 | (0.62,15.16) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1129 |
| No | 572 | 1 | 0.2 | 578 | 6 | 1.0 | 0.0797 | 4.27 | (0.73,25.16) | 4.31 | (0.73,25.56) | 0.01 | ( 0.00, 0.02) | |
| Yes | 2703 | 18 | 0.7 | 2752 | 17 | 0.6 | 0.8184 | 0.93 | (0.48, 1.79) | 0.93 | (0.48, 1.80) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.0722 |
| No | 344 | 4 | 1.2 | 349 | 0 | 0 | 0.0920 | 0.19 | (0.02, 1.65) | 0.19 | (0.02, 1.63) | -0.01 | (-0.03, 0.00) | |
| Yes | 2931 | 15 | 0.5 | 2981 | 23 | 0.8 | 0.2142 | 1.50 | (0.79, 2.88) | 1.51 | (0.79, 2.90) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.7222 |
| No | 275 | 2 | 0.7 | 307 | 2 | 0.7 | 0.8781 | 0.87 | (0.15, 5.09) | 0.87 | (0.15, 5.12) | 0.00 | (-0.02, 0.01) | |
| Yes | 3000 | 17 | 0.6 | 3023 | 21 | 0.7 | 0.5334 | 1.22 | (0.65, 2.32) | 1.23 | (0.65, 2.33) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 85 | 2.6 | 3330 | 102 | 3.1 | 0.2524 | 1.18 | (0.89, 1.57) | 1.19 | (0.89, 1.59) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.8813 |
| 1245.110 | 2001 | 52 | 2.6 | 2052 | 64 | 3.1 | 0.3208 | 1.20 | (0.84, 1.72) | 1.21 | (0.83, 1.75) | 0.01 | (-0.01, 0.02) | |
| 1245.121 | 1274 | 33 | 2.6 | 1278 | 38 | 3.0 | 0.5563 | 1.15 | (0.72, 1.82) | 1.15 | (0.72, 1.85) | 0.00 | (-0.01, 0.02) | |
| Sex | | | | | | | | | | | | | | 0.3630 |
| Male | 2023 | 60 | 3.0 | 2068 | 66 | 3.2 | 0.6773 | 1.08 | (0.76, 1.52) | 1.08 | (0.76, 1.54) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 25 | 2.0 | 1262 | 36 | 2.9 | 0.1634 | 1.43 | (0.86, 2.36) | 1.44 | (0.86, 2.41) | 0.01 | ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.3055 |
| <65 | 766 | 16 | 2.1 | 705 | 12 | 1.7 | 0.5980 | 0.82 | (0.39, 1.72) | 0.82 | (0.38, 1.74) | 0.00 | (-0.02, 0.01) | |
| >=65 | 2509 | 69 | 2.8 | 2625 | 90 | 3.4 | 0.1605 | 1.25 | (0.92, 1.70) | 1.26 | (0.91, 1.73) | 0.01 | ( 0.00, 0.02) | |
| Region | | | | | | | | | | | | | | 0.3004 |
| North America | 434 | 29 | 6.7 | 432 | 35 | 8.1 | 0.4249 | 1.21 | (0.75, 1.95) | 1.23 | (0.74, 2.05) | 0.01 | (-0.02, 0.05) | |
| Latin America | 931 | 13 | 1.4 | 944 | 26 | 2.8 | 0.0400 | 1.97 | (1.02, 3.79) | 1.99 | (1.02, 3.90) | 0.01 | ( 0.00, 0.03) | |
| Europe | 1334 | 28 | 2.1 | 1361 | 30 | 2.2 | 0.8548 | 1.05 | (0.63, 1.74) | 1.05 | (0.62, 1.77) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 7 | 1.7 | 413 | 7 | 1.7 | 0.9999 | 1.00 | (0.35, 2.82) | 1.00 | (0.35, 2.88) | 0.00 | (-0.02, 0.02) | |
| Other | 171 | 8 | 4.7 | 180 | 4 | 2.2 | 0.2163 | 0.50 | (0.16, 1.54) | 0.48 | (0.15, 1.55) | -0.02 | (-0.06, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7310 |
| Diabetic | 1739 | 51 | 2.9 | 1779 | 59 | 3.3 | 0.5120 | 1.13 | (0.78, 1.64) | 1.14 | (0.78, 1.66) | 0.00 | (-0.01, 0.02) | |
| Non-Diabetic | 1536 | 34 | 2.2 | 1551 | 43 | 2.8 | 0.3209 | 1.25 | (0.80, 1.95) | 1.26 | (0.80, 1.99) | 0.01 | (-0.01, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2292 |
| <30 | 1975 | 43 | 2.2 | 1930 | 58 | 3.0 | 0.1022 | 1.38 | (0.94, 2.04) | 1.39 | (0.93, 2.08) | 0.01 | ( 0.00, 0.02) | |
| >=30 | 1300 | 42 | 3.2 | 1400 | 44 | 3.1 | 0.9020 | 0.97 | (0.64, 1.48) | 0.97 | (0.63, 1.50) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3453 |
| <130 | 1684 | 44 | 2.6 | 1687 | 59 | 3.5 | 0.1332 | 1.34 | (0.91, 1.97) | 1.35 | (0.91, 2.01) | 0.01 | ( 0.00, 0.02) | |
| >=130 | 1591 | 41 | 2.6 | 1643 | 43 | 2.6 | 0.9311 | 1.02 | (0.67, 1.55) | 1.02 | (0.66, 1.57) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8972 |
| <75 | 1653 | 49 | 3.0 | 1612 | 60 | 3.7 | 0.2289 | 1.26 | (0.87, 1.82) | 1.27 | (0.86, 1.86) | 0.01 | ( 0.00, 0.02) | |
| 75 to <85 | 1005 | 27 | 2.7 | 1085 | 32 | 2.9 | 0.7165 | 1.10 | (0.66, 1.82) | 1.10 | (0.65, 1.85) | 0.00 | (-0.01, 0.02) | |
| >=85 | 617 | 9 | 1.5 | 633 | 10 | 1.6 | 0.8568 | 1.09 | (0.44, 2.65) | 1.09 | (0.44, 2.70) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0703 |
| <30 | 250 | 6 | 2.4 | 263 | 20 | 7.6 | 0.0084 | 3.15 | (1.27, 7.78) | 3.32 | (1.30, 8.46) | 0.05 | ( 0.01, 0.09) | |
| 30 to <45 | 898 | 29 | 3.2 | 909 | 30 | 3.3 | 0.9371 | 1.02 | (0.62, 1.68) | 1.02 | (0.61, 1.72) | 0.00 | (-0.02, 0.02) | |
| >=45 | 2126 | 50 | 2.4 | 2158 | 52 | 2.4 | 0.9023 | 1.02 | (0.70, 1.50) | 1.02 | (0.69, 1.52) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2524 |
| Normal (<30) | 1216 | 29 | 2.4 | 1243 | 33 | 2.7 | 0.6713 | 1.11 | (0.68, 1.82) | 1.12 | (0.67, 1.85) | 0.00 | (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 40 | 2.6 | 1546 | 57 | 3.7 | 0.0796 | 1.42 | (0.96, 2.12) | 1.44 | (0.96, 2.17) | 0.01 | ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 500 | 16 | 3.2 | 525 | 12 | 2.3 | 0.3583 | 0.71 | (0.34, 1.48) | 0.70 | (0.33, 1.50) | -0.01 | (-0.03, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0087 |
| Low, moderate or high | 2430 | 63 | 2.6 | 2495 | 58 | 2.3 | 0.5442 | 0.90 | (0.63, 1.28) | 0.89 | (0.62, 1.28) | 0.00 | (-0.01, 0.01) | |
| Very high | 834 | 22 | 2.6 | 820 | 44 | 5.4 | 0.0045 | 2.04 | (1.23, 3.38) | 2.10 | (1.25, 3.54) | 0.03 | ( 0.01, 0.05) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5942 |
| No | 572 | 19 | 3.3 | 578 | 26 | 4.5 | 0.3025 | 1.36 | (0.76, 2.42) | 1.37 | (0.75, 2.51) | 0.01 | (-0.01, 0.03) | |
| Yes | 2703 | 66 | 2.4 | 2752 | 76 | 2.8 | 0.4572 | 1.13 | (0.82, 1.57) | 1.14 | (0.81, 1.59) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6137 |
| No | 344 | 12 | 3.5 | 349 | 12 | 3.4 | 0.9525 | 0.98 | (0.45, 2.13) | 0.98 | (0.43, 2.20) | 0.00 | (-0.03, 0.03) | |
| Yes | 2931 | 73 | 2.5 | 2981 | 90 | 3.0 | 0.2156 | 1.21 | (0.89, 1.64) | 1.22 | (0.89, 1.67) | 0.01 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6681 |
| No | 275 | 4 | 1.5 | 307 | 7 | 2.3 | 0.4813 | 1.51 | (0.48, 4.79) | 1.52 | (0.47, 4.96) | 0.01 | (-0.01, 0.03) | |
| Yes | 3000 | 81 | 2.7 | 3023 | 95 | 3.1 | 0.3082 | 1.16 | (0.87, 1.56) | 1.17 | (0.87, 1.58) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 72 | 2.2 | 3330 | 88 | 2.6 | 0.2411 | 1.20 | (0.88, 1.63) | 1.21 | (0.88, 1.65) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.5511 |
| 1245.110 | 2001 | 43 | 2.1 | 2052 | 57 | 2.8 | 0.1970 | 1.29 | (0.87, 1.91) | 1.30 | (0.87, 1.94) | 0.01 | ( 0.00, 0.02) | |
| 1245.121 | 1274 | 29 | 2.3 | 1278 | 31 | 2.4 | 0.8034 | 1.07 | (0.65, 1.76) | 1.07 | (0.64, 1.78) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.8041 |
| Male | 2023 | 51 | 2.5 | 2068 | 61 | 2.9 | 0.4018 | 1.17 | (0.81, 1.69) | 1.17 | (0.81, 1.71) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 21 | 1.7 | 1262 | 27 | 2.1 | 0.3996 | 1.27 | (0.72, 2.24) | 1.28 | (0.72, 2.27) | 0.00 | (-0.01, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.2653 |
| <65 | 766 | 15 | 2.0 | 705 | 11 | 1.6 | 0.5706 | 0.80 | (0.37, 1.73) | 0.80 | (0.36, 1.75) | 0.00 | (-0.02, 0.01) | |
| >=65 | 2509 | 57 | 2.3 | 2625 | 77 | 2.9 | 0.1370 | 1.29 | (0.92, 1.81) | 1.30 | (0.92, 1.84) | 0.01 | ( 0.00, 0.02) | |
| Region | | | | | | | | | | | | | | 0.6957 |
| North America | 434 | 27 | 6.2 | 432 | 31 | 7.2 | 0.5748 | 1.15 | (0.70, 1.90) | 1.17 | (0.68, 1.99) | 0.01 | (-0.02, 0.04) | |
| Latin America | 931 | 11 | 1.2 | 944 | 21 | 2.2 | 0.0826 | 1.87 | (0.91, 3.86) | 1.89 | (0.91, 3.95) | 0.01 | ( 0.00, 0.02) | |
| Europe | 1334 | 23 | 1.7 | 1361 | 26 | 1.9 | 0.7197 | 1.11 | (0.64, 1.93) | 1.11 | (0.63, 1.95) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 6 | 1.5 | 413 | 6 | 1.5 | 0.9981 | 1.00 | (0.32, 3.09) | 1.00 | (0.32, 3.14) | 0.00 | (-0.02, 0.02) | |
| Other | 171 | 5 | 2.9 | 180 | 4 | 2.2 | 0.6542 | 0.76 | (0.22, 2.57) | 0.75 | (0.21, 2.66) | -0.01 | (-0.04, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9312 |
| Diabetic | 1739 | 42 | 2.4 | 1779 | 51 | 2.9 | 0.4030 | 1.19 | (0.79, 1.78) | 1.19 | (0.79, 1.80) | 0.00 | (-0.01, 0.02) | |
| Non-Diabetic | 1536 | 30 | 2.0 | 1551 | 37 | 2.4 | 0.4115 | 1.22 | (0.76, 1.97) | 1.23 | (0.75, 1.99) | 0.00 | (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4993 |
| <30 | 1975 | 38 | 1.9 | 1930 | 49 | 2.5 | 0.1911 | 1.32 | (0.87, 2.01) | 1.33 | (0.87, 2.04) | 0.01 | ( 0.00, 0.02) | |
| >=30 | 1300 | 34 | 2.6 | 1400 | 39 | 2.8 | 0.7753 | 1.07 | (0.68, 1.68) | 1.07 | (0.67, 1.71) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3517 |
| <130 | 1684 | 37 | 2.2 | 1687 | 51 | 3.0 | 0.1312 | 1.38 | (0.91, 2.09) | 1.39 | (0.90, 2.13) | 0.01 | ( 0.00, 0.02) | |
| >=130 | 1591 | 35 | 2.2 | 1643 | 37 | 2.3 | 0.9098 | 1.03 | (0.65, 1.62) | 1.03 | (0.64, 1.64) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7180 |
| <75 | 1653 | 40 | 2.4 | 1612 | 52 | 3.2 | 0.1654 | 1.33 | (0.89, 2.00) | 1.34 | (0.88, 2.04) | 0.01 | ( 0.00, 0.02) | |
| 75 to <85 | 1005 | 24 | 2.4 | 1085 | 26 | 2.4 | 0.9895 | 1.00 | (0.58, 1.74) | 1.00 | (0.57, 1.76) | 0.00 | (-0.01, 0.01) | |
| >=85 | 617 | 8 | 1.3 | 633 | 10 | 1.6 | 0.6714 | 1.22 | (0.48, 3.07) | 1.22 | (0.48, 3.12) | 0.00 | (-0.01, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1135 |
| <30 | 250 | 4 | 1.6 | 263 | 15 | 5.7 | 0.0144 | 3.61 | (1.19,10.91) | 3.76 | (1.22,11.61) | 0.04 | ( 0.01, 0.07) | |
| 30 to <45 | 898 | 25 | 2.8 | 909 | 27 | 3.0 | 0.8146 | 1.07 | (0.62, 1.82) | 1.07 | (0.62, 1.85) | 0.00 | (-0.01, 0.02) | |
| >=45 | 2126 | 43 | 2.0 | 2158 | 46 | 2.1 | 0.8060 | 1.05 | (0.70, 1.59) | 1.05 | (0.69, 1.61) | 0.00 | (-0.01, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5451 |
| Normal (<30) | 1216 | 24 | 2.0 | 1243 | 32 | 2.6 | 0.3194 | 1.30 | (0.77, 2.20) | 1.31 | (0.77, 2.24) | 0.01 | (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 35 | 2.3 | 1546 | 45 | 2.9 | 0.2595 | 1.28 | (0.83, 1.99) | 1.29 | (0.83, 2.02) | 0.01 | ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 500 | 13 | 2.6 | 525 | 11 | 2.1 | 0.5749 | 0.80 | (0.36, 1.76) | 0.79 | (0.35, 1.79) | -0.01 | (-0.02, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0236 |
| Low, moderate or high | 2430 | 54 | 2.2 | 2495 | 52 | 2.1 | 0.7388 | 0.94 | (0.64, 1.37) | 0.94 | (0.64, 1.38) | 0.00 | (-0.01, 0.01) | |
| Very high | 834 | 18 | 2.2 | 820 | 36 | 4.4 | 0.0104 | 2.04 | (1.17, 3.57) | 2.09 | (1.18, 3.72) | 0.02 | ( 0.01, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4828 |
| No | 572 | 14 | 2.4 | 578 | 21 | 3.6 | 0.2422 | 1.49 | (0.76, 2.90) | 1.50 | (0.76, 2.99) | 0.01 | (-0.01, 0.03) | |
| Yes | 2703 | 58 | 2.1 | 2752 | 67 | 2.4 | 0.4770 | 1.13 | (0.80, 1.61) | 1.14 | (0.80, 1.62) | 0.00 | (-0.01, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7481 |
| No | 344 | 11 | 3.2 | 349 | 12 | 3.4 | 0.8813 | 1.06 | (0.48, 2.36) | 1.06 | (0.47, 2.44) | 0.00 | (-0.02, 0.03) | |
| Yes | 2931 | 61 | 2.1 | 2981 | 76 | 2.5 | 0.2328 | 1.22 | (0.88, 1.71) | 1.23 | (0.87, 1.73) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6011 |
| No | 275 | 3 | 1.1 | 307 | 6 | 2.0 | 0.4249 | 1.68 | (0.46, 6.08) | 1.69 | (0.46, 6.27) | 0.01 | (-0.01, 0.03) | |
| Yes | 3000 | 69 | 2.3 | 3023 | 82 | 2.7 | 0.3066 | 1.18 | (0.86, 1.62) | 1.18 | (0.86, 1.64) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 268 | 8.2 | 3330 | 203 | 6.1 | 0.0009 | 0.74 | (0.62, 0.89) | 0.73 | (0.60, 0.88) | -0.02 | (-0.03,-0.01) | |
| Study | | | | | | | | | | | | | | 0.3558 |
| 1245.110 | 2001 | 173 | 8.6 | 2052 | 140 | 6.8 | 0.0297 | 0.79 | (0.64, 0.98) | 0.77 | (0.61, 0.98) | -0.02 | (-0.03, 0.00) | |
| 1245.121 | 1274 | 95 | 7.5 | 1278 | 63 | 4.9 | 0.0081 | 0.66 | (0.49, 0.90) | 0.64 | (0.46, 0.89) | -0.03 | (-0.04,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.2660 |
| Male | 2023 | 172 | 8.5 | 2068 | 121 | 5.9 | 0.0010 | 0.69 | (0.55, 0.86) | 0.67 | (0.52, 0.85) | -0.03 | (-0.04,-0.01) | |
| Female | 1252 | 96 | 7.7 | 1262 | 82 | 6.5 | 0.2444 | 0.84 | (0.64, 1.12) | 0.83 | (0.61, 1.13) | -0.01 | (-0.03, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6441 |
| <65 | 766 | 66 | 8.6 | 705 | 42 | 6.0 | 0.0499 | 0.69 | (0.47,>1.00) | 0.67 | (0.45, 1.00) | -0.03 | (-0.05, 0.00) | |
| >=65 | 2509 | 202 | 8.1 | 2625 | 161 | 6.1 | 0.0075 | 0.76 | (0.62, 0.93) | 0.75 | (0.60, 0.93) | -0.02 | (-0.03,-0.01) | |
| Region | | | | | | | | | | | | | | 0.6857 |
| North America | 434 | 73 | 16.8 | 432 | 63 | 14.6 | 0.3625 | 0.87 | (0.64, 1.18) | 0.84 | (0.58, 1.22) | -0.02 | (-0.07, 0.03) | |
| Latin America | 931 | 73 | 7.8 | 944 | 57 | 6.0 | 0.1276 | 0.77 | (0.55, 1.08) | 0.76 | (0.53, 1.08) | -0.02 | (-0.04, 0.01) | |
| Europe | 1334 | 90 | 6.7 | 1361 | 57 | 4.2 | 0.0035 | 0.62 | (0.45, 0.86) | 0.60 | (0.43, 0.85) | -0.03 | (-0.04,-0.01) | |
| Asia | 405 | 15 | 3.7 | 413 | 11 | 2.7 | 0.3636 | 0.70 | (0.33, 1.51) | 0.69 | (0.31, 1.53) | -0.01 | (-0.04, 0.01) | |
| Other | 171 | 17 | 9.9 | 180 | 15 | 8.3 | 0.5505 | 0.82 | (0.43, 1.57) | 0.80 | (0.39, 1.65) | -0.02 | (-0.08, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2824 |
| Diabetic | 1739 | 158 | 9.1 | 1779 | 130 | 7.3 | 0.0512 | 0.80 | (0.64,>1.00) | 0.79 | (0.62, 1.00) | -0.02 | (-0.04, 0.00) | |
| Non-Diabetic | 1536 | 110 | 7.2 | 1551 | 73 | 4.7 | 0.0039 | 0.66 | (0.49, 0.88) | 0.64 | (0.47, 0.87) | -0.02 | (-0.04,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1546 |
| <30 | 1975 | 142 | 7.2 | 1930 | 90 | 4.7 | 0.0008 | 0.65 | (0.50, 0.84) | 0.63 | (0.48, 0.83) | -0.03 | (-0.04,-0.01) | |
| >=30 | 1300 | 126 | 9.7 | 1400 | 113 | 8.1 | 0.1445 | 0.84 | (0.66, 1.06) | 0.82 | (0.63, 1.07) | -0.02 | (-0.04, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8531 |
| <130 | 1684 | 142 | 8.4 | 1687 | 108 | 6.4 | 0.0232 | 0.76 | (0.59, 0.96) | 0.74 | (0.57, 0.96) | -0.02 | (-0.04, 0.00) | |
| >=130 | 1591 | 126 | 7.9 | 1643 | 95 | 5.8 | 0.0170 | 0.73 | (0.57, 0.95) | 0.72 | (0.54, 0.94) | -0.02 | (-0.04, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9026 |
| <75 | 1653 | 162 | 9.8 | 1612 | 121 | 7.5 | 0.0186 | 0.76 | (0.61, 0.96) | 0.74 | (0.58, 0.95) | -0.02 | (-0.04, 0.00) | |
| 75 to <85 | 1005 | 70 | 7.0 | 1085 | 53 | 4.9 | 0.0443 | 0.70 | (0.50, 0.99) | 0.69 | (0.48, 0.99) | -0.02 | (-0.04, 0.00) | |
| >=85 | 617 | 36 | 5.8 | 633 | 29 | 4.6 | 0.3260 | 0.79 | (0.49, 1.27) | 0.78 | (0.47, 1.29) | -0.01 | (-0.04, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4661 |
| <30 | 250 | 47 | 18.8 | 263 | 44 | 16.7 | 0.6630 | 0.92 | (0.63, 1.34) | 0.90 | (0.57, 1.43) | -0.01 | (-0.08, 0.05) | |
| 30 to <45 | 898 | 93 | 10.4 | 909 | 65 | 7.2 | 0.0153 | 0.69 | (0.51, 0.93) | 0.66 | (0.48, 0.93) | -0.03 | (-0.06,-0.01) | |
| >=45 | 2126 | 128 | 6.0 | 2158 | 94 | 4.4 | 0.0135 | 0.72 | (0.56, 0.94) | 0.71 | (0.54, 0.93) | -0.02 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.0661 |
| Normal (<30) | 1216 | 86 | 7.1 | 1243 | 61 | 4.9 | 0.0236 | 0.69 | (0.50, 0.95) | 0.68 | (0.48, 0.95) | -0.02 | (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 131 | 8.5 | 1546 | 86 | 5.6 | 0.0014 | 0.65 | (0.50, 0.85) | 0.63 | (0.48, 0.84) | -0.03 | (-0.05,-0.01) | |
| Macroalbuminuria (>300) | 500 | 49 | 9.8 | 525 | 56 | 10.7 | 0.6202 | 1.10 | (0.76, 1.58) | 1.11 | (0.74, 1.66) | 0.01 | (-0.03, 0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1835 |
| Low, moderate or high | 2430 | 155 | 6.4 | 2495 | 109 | 4.4 | 0.0017 | 0.68 | (0.54, 0.87) | 0.67 | (0.52, 0.86) | -0.02 | (-0.03,-0.01) | |
| Very high | 834 | 111 | 13.3 | 820 | 94 | 11.5 | 0.2768 | 0.87 | (0.67, 1.12) | 0.85 | (0.63, 1.14) | -0.02 | (-0.05, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6821 |
| No | 572 | 52 | 9.1 | 578 | 42 | 7.3 | 0.2621 | 0.80 | (0.54, 1.18) | 0.78 | (0.51, 1.20) | -0.02 | (-0.05, 0.01) | |
| Yes | 2703 | 216 | 8.0 | 2752 | 161 | 5.9 | 0.0017 | 0.73 | (0.60, 0.89) | 0.71 | (0.58, 0.88) | -0.02 | (-0.03,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2004 |
| No | 344 | 35 | 10.2 | 349 | 19 | 5.4 | 0.0199 | 0.53 | (0.31, 0.91) | 0.51 | (0.28, 0.91) | -0.05 | (-0.09,-0.01) | |
| Yes | 2931 | 233 | 7.9 | 2981 | 184 | 6.2 | 0.0071 | 0.77 | (0.64, 0.93) | 0.76 | (0.62, 0.93) | -0.02 | (-0.03, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1030 |
| No | 275 | 17 | 6.2 | 307 | 7 | 2.3 | 0.0191 | 0.37 | (0.16, 0.88) | 0.36 | (0.15, 0.87) | -0.04 | (-0.07,-0.01) | |
| Yes | 3000 | 251 | 8.4 | 3023 | 196 | 6.5 | 0.0051 | 0.77 | (0.65, 0.93) | 0.76 | (0.62, 0.92) | -0.02 | (-0.03,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 10 | 0.3 | 3330 | 6 | 0.2 | 0.2994 | 0.59 | (0.21, 1.62) | 0.59 | (0.21, 1.62) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.3522 |
| 1245.110 | 2001 | 6 | 0.3 | 2052 | 5 | 0.2 | 0.7311 | 0.81 | (0.25, 2.66) | 0.81 | (0.25, 2.67) | 0.00 | ( 0.00, 0.00) | |
| 1245.121 | 1274 | 4 | 0.3 | 1278 | 1 | 0.1 | 0.1782 | 0.25 | (0.03, 2.23) | 0.25 | (0.03, 2.23) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4185 |
| Male | 2023 | 6 | 0.3 | 2068 | 5 | 0.2 | 0.7349 | 0.81 | (0.25, 2.67) | 0.81 | (0.25, 2.67) | 0.00 | ( 0.00, 0.00) | |
| Female | 1252 | 4 | 0.3 | 1262 | 1 | 0.1 | 0.2142 | 0.33 | (0.05, 2.08) | 0.33 | (0.05, 2.09) | 0.00 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.5353 |
| <65 | 766 | 1 | 0.1 | 705 | 1 | 0.1 | 0.9364 | 1.08 | (0.15, 7.77) | 1.08 | (0.15, 7.76) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 9 | 0.4 | 2625 | 5 | 0.2 | 0.2485 | 0.53 | (0.18, 1.58) | 0.53 | (0.18, 1.59) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | |
| North America | 434 | 4 | 0.9 | 432 | 4 | 0.9 | | | | | | | | |
| Latin America | 931 | 0 | 0 | 944 | 0 | 0 | | | | | | | | |
| Europe | 1334 | 3 | 0.2 | 1361 | 0 | 0 | | | | | | | | |
| Asia | 405 | 3 | 0.7 | 413 | 1 | 0.2 | | | | | | | | |
| Other | 171 | 0 | 0 | 180 | 1 | 0.6 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8743 |
| Diabetic | 1739 | 3 | 0.2 | 1779 | 2 | 0.1 | 0.6610 | 0.70 | (0.14, 3.51) | 0.70 | (0.14, 3.53) | 0.00 | ( 0.00, 0.00) | |
| Non-Diabetic | 1536 | 7 | 0.5 | 1551 | 4 | 0.3 | 0.3771 | 0.59 | (0.18, 1.91) | 0.59 | (0.18, 1.91) | 0.00 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8979 |
| <30 | 1975 | 7 | 0.4 | 1930 | 4 | 0.2 | 0.3808 | 0.58 | (0.17, 1.99) | 0.58 | (0.17, 1.99) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1300 | 3 | 0.2 | 1400 | 2 | 0.1 | 0.6152 | 0.66 | (0.13, 3.33) | 0.66 | (0.13, 3.35) | 0.00 | ( 0.00, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | |
| <130 | 1684 | 6 | 0.4 | 1687 | 3 | 0.2 | | | | | | | | |
| >=130 | 1591 | 4 | 0.3 | 1643 | 3 | 0.2 | | | | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5406 |
| <75 | 1653 | 7 | 0.4 | 1612 | 4 | 0.2 | 0.3842 | 0.58 | (0.17, 1.99) | 0.58 | (0.17, 2.00) | 0.00 | (-0.01, 0.00) | |
| 75 to <85 | 1005 | 2 | 0.2 | 1085 | 0 | 0 | 0.2823 | 0.31 | (0.03, 2.98) | 0.31 | (0.03, 2.98) | 0.00 | (-0.01, 0.00) | |
| >=85 | 617 | 1 | 0.2 | 633 | 2 | 0.3 | 0.6766 | 1.46 | (0.25, 8.63) | 1.46 | (0.24, 8.71) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | |
| <30 | 250 | 1 | 0.4 | 263 | 2 | 0.8 | | | | | | | | |
| 30 to <45 | 898 | 5 | 0.6 | 909 | 1 | 0.1 | | | | | | | | |
| >=45 | 2126 | 4 | 0.2 | 2158 | 3 | 0.1 | | | | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | |
| Normal (<30) | 1216 | 6 | 0.5 | 1243 | 2 | 0.2 | | | | | | | | |
| Microalbuminuria (30 to <=300) | 1548 | 4 | 0.3 | 1546 | 2 | 0.1 | | | | | | | | |
| Macroalbuminuria (>300) | 500 | 0 | 0 | 525 | 2 | 0.4 | | | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2272 |
| Low, moderate or high | 2430 | 8 | 0.3 | 2495 | 3 | 0.1 | 0.1347 | 0.40 | (0.11, 1.39) | 0.40 | (0.11, 1.39) | 0.00 | ( 0.00, 0.00) | |
| Very high | 834 | 2 | 0.2 | 820 | 3 | 0.4 | 0.6416 | 1.52 | (0.26, 9.03) | 1.52 | (0.25, 9.12) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7613 |
| No | 572 | 4 | 0.7 | 578 | 2 | 0.3 | 0.3993 | 0.49 | (0.09, 2.66) | 0.49 | (0.09, 2.68) | 0.00 | (-0.01, 0.00) | |
| Yes | 2703 | 6 | 0.2 | 2752 | 4 | 0.1 | 0.5214 | 0.68 | (0.20, 2.25) | 0.68 | (0.20, 2.25) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9468 |
| No | 344 | 2 | 0.6 | 349 | 1 | 0.3 | 0.5709 | 0.57 | (0.08, 4.15) | 0.56 | (0.07, 4.25) | 0.00 | (-0.01, 0.01) | |
| Yes | 2931 | 8 | 0.3 | 2981 | 5 | 0.2 | 0.3842 | 0.61 | (0.20, 1.87) | 0.61 | (0.20, 1.87) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
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Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8040 |
| No | 275 | 0 | 0 | 307 | 0 | 0 | 0.9161 | 0.86 | (0.05,13.65) | 0.86 | (0.05,13.88) | 0.00 | (-0.01, 0.01) | |
| Yes | 3000 | 10 | 0.3 | 3023 | 6 | 0.2 | 0.3074 | 0.59 | (0.22, 1.63) | 0.59 | (0.22, 1.63) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 12 | 0.4 | 3330 | 14 | 0.4 | 0.7261 | 1.15 | (0.53, 2.47) | 1.15 | (0.53, 2.48) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.1889 |
| 1245.110 | 2001 | 9 | 0.4 | 2052 | 7 | 0.3 | 0.5814 | 0.76 | (0.28, 2.03) | 0.76 | (0.28, 2.04) | 0.00 | ( 0.00, 0.00) | |
| 1245.121 | 1274 | 3 | 0.2 | 1278 | 7 | 0.5 | 0.2069 | 2.33 | (0.60, 8.97) | 2.33 | (0.60, 9.04) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.5696 |
| Male | 2023 | 9 | 0.4 | 2068 | 9 | 0.4 | 0.9623 | 0.98 | (0.39, 2.46) | 0.98 | (0.39, 2.47) | 0.00 | ( 0.00, 0.00) | |
| Female | 1252 | 3 | 0.2 | 1262 | 5 | 0.4 | 0.5065 | 1.56 | (0.41, 5.92) | 1.57 | (0.41, 5.97) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.2274 |
| <65 | 766 | 2 | 0.3 | 705 | 5 | 0.7 | 0.2122 | 2.71 | (0.53,13.92) | 2.73 | (0.53,14.08) | 0.00 | ( 0.00, 0.01) | |
| >=65 | 2509 | 10 | 0.4 | 2625 | 9 | 0.3 | 0.7430 | 0.86 | (0.35, 2.12) | 0.86 | (0.35, 2.12) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | |
| North America | 434 | 2 | 0.5 | 432 | 6 | 1.4 | | | | | | | | |
| Latin America | 931 | 4 | 0.4 | 944 | 3 | 0.3 | | | | | | | | |
| Europe | 1334 | 4 | 0.3 | 1361 | 2 | 0.1 | | | | | | | | |
| Asia | 405 | 0 | 0 | 413 | 1 | 0.2 | | | | | | | | |
| Other | 171 | 2 | 1.2 | 180 | 2 | 1.1 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9247 |
| Diabetic | 1739 | 12 | 0.7 | 1779 | 14 | 0.8 | 0.7379 | 1.14 | (0.53, 2.45) | 1.14 | (0.53, 2.47) | 0.00 | ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 0 | 0 | 1551 | 0 | 0 | 0.9956 | 0.99 | (0.06,15.85) | 0.99 | (0.06,15.88) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5336 |
| <30 | 1975 | 4 | 0.2 | 1930 | 6 | 0.3 | 0.4920 | 1.55 | (0.44, 5.46) | 1.55 | (0.44, 5.50) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1300 | 8 | 0.6 | 1400 | 8 | 0.6 | 0.8900 | 0.93 | (0.35, 2.49) | 0.93 | (0.35, 2.50) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4532 |
| <130 | 1684 | 7 | 0.4 | 1687 | 6 | 0.4 | 0.7692 | 0.85 | (0.29, 2.52) | 0.85 | (0.29, 2.53) | 0.00 | ( 0.00, 0.00) | |
| >=130 | 1591 | 5 | 0.3 | 1643 | 8 | 0.5 | 0.4432 | 1.54 | (0.50, 4.73) | 1.55 | (0.50, 4.74) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6147 |
| <75 | 1653 | 7 | 0.4 | 1612 | 5 | 0.3 | 0.5921 | 0.73 | (0.23, 2.29) | 0.73 | (0.23, 2.31) | 0.00 | (-0.01, 0.00) | |
| 75 to <85 | 1005 | 5 | 0.5 | 1085 | 8 | 0.7 | 0.4850 | 1.48 | (0.49, 4.53) | 1.49 | (0.48, 4.57) | 0.00 | ( 0.00, 0.01) | |
| >=85 | 617 | 0 | 0 | 633 | 1 | 0.2 | 0.5846 | 1.93 | (0.17,21.33) | 1.94 | (0.17,21.46) | 0.00 | ( 0.00, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1749 |
| <30 | 250 | 1 | 0.4 | 263 | 4 | 1.5 | 0.2579 | 2.81 | (0.43,18.17) | 2.84 | (0.44,18.45) | 0.01 | (-0.01, 0.03) | |
| 30 to <45 | 898 | 2 | 0.2 | 909 | 5 | 0.6 | 0.2621 | 2.48 | (0.48,12.74) | 2.48 | (0.48,12.84) | 0.00 | ( 0.00, 0.01) | |
| >=45 | 2126 | 9 | 0.4 | 2158 | 5 | 0.2 | 0.2704 | 0.55 | (0.19, 1.62) | 0.55 | (0.18, 1.63) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5318 |
| Normal (<30) | 1216 | 4 | 0.3 | 1243 | 2 | 0.2 | 0.3981 | 0.49 | (0.09, 2.66) | 0.49 | (0.09, 2.67) | 0.00 | (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 5 | 0.3 | 1546 | 7 | 0.5 | 0.5700 | 1.39 | (0.44, 4.37) | 1.39 | (0.44, 4.40) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 500 | 3 | 0.6 | 525 | 5 | 1.0 | 0.5368 | 1.57 | (0.37, 6.60) | 1.57 | (0.37, 6.64) | 0.00 | (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2230 |
| Low, moderate or high | 2430 | 8 | 0.3 | 2495 | 6 | 0.2 | 0.5616 | 0.73 | (0.26, 2.10) | 0.73 | (0.25, 2.11) | 0.00 | ( 0.00, 0.00) | |
| Very high | 834 | 4 | 0.5 | 820 | 8 | 1.0 | 0.2525 | 1.93 | (0.61, 6.09) | 1.94 | (0.61, 6.13) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5110 |
| No | 572 | 2 | 0.3 | 578 | 4 | 0.7 | 0.4569 | 1.78 | (0.38, 8.35) | 1.79 | (0.38, 8.44) | 0.00 | (-0.01, 0.01) | |
| Yes | 2703 | 10 | 0.4 | 2752 | 10 | 0.4 | 0.9705 | 0.98 | (0.41, 2.35) | 0.98 | (0.41, 2.36) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4595 |
| No | 344 | 2 | 0.6 | 349 | 1 | 0.3 | 0.5709 | 0.57 | (0.08, 4.15) | 0.56 | (0.07, 4.25) | 0.00 | (-0.01, 0.01) | |
| Yes | 2931 | 10 | 0.3 | 2981 | 13 | 0.4 | 0.5589 | 1.28 | (0.56, 2.90) | 1.28 | (0.56, 2.91) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8136 |
| No | 275 | 1 | 0.4 | 307 | 1 | 0.3 | 0.9113 | 0.88 | (0.09, 8.39) | 0.88 | (0.09, 8.51) | 0.00 | (-0.01, 0.01) | |
| Yes | 3000 | 11 | 0.4 | 3023 | 13 | 0.4 | 0.6959 | 1.17 | (0.53, 2.61) | 1.17 | (0.53, 2.62) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 30 | 0.9 | 3330 | 15 | 0.5 | 0.0209 | 0.49 | (0.26, 0.91) | 0.49 | (0.26, 0.91) | 0.00 | (-0.01, 0.00) | |
| Study | | | | | | | | | | | | | | 0.1742 |
| 1245.110 | 2001 | 20 | 1.0 | 2052 | 13 | 0.6 | 0.1950 | 0.63 | (0.32, 1.27) | 0.63 | (0.31, 1.27) | 0.00 | (-0.01, 0.00) | |
| 1245.121 | 1274 | 10 | 0.8 | 1278 | 2 | 0.2 | 0.0203 | 0.20 | (0.04, 0.91) | 0.20 | (0.04, 0.91) | -0.01 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.9238 |
| Male | 2023 | 22 | 1.1 | 2068 | 11 | 0.5 | 0.0466 | 0.49 | (0.24,>1.00) | 0.49 | (0.23, 1.00) | -0.01 | (-0.01, 0.00) | |
| Female | 1252 | 8 | 0.6 | 1262 | 4 | 0.3 | 0.2553 | 0.52 | (0.17, 1.63) | 0.52 | (0.17, 1.64) | 0.00 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.3901 |
| <65 | 766 | 8 | 1.0 | 705 | 2 | 0.3 | 0.0742 | 0.27 | (0.06, 1.26) | 0.27 | (0.06, 1.26) | -0.01 | (-0.02, 0.00) | |
| >=65 | 2509 | 22 | 0.9 | 2625 | 13 | 0.5 | 0.0976 | 0.57 | (0.29, 1.12) | 0.56 | (0.28, 1.12) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.5419 |
| North America | 434 | 6 | 1.4 | 432 | 4 | 0.9 | 0.5480 | 0.69 | (0.21, 2.30) | 0.69 | (0.21, 2.32) | 0.00 | (-0.02, 0.01) | |
| Latin America | 931 | 9 | 1.0 | 944 | 5 | 0.5 | 0.2838 | 0.56 | (0.19, 1.65) | 0.55 | (0.18, 1.66) | 0.00 | (-0.01, 0.00) | |
| Europe | 1334 | 10 | 0.7 | 1361 | 2 | 0.1 | 0.0196 | 0.20 | (0.04, 0.90) | 0.20 | (0.04, 0.90) | -0.01 | (-0.01, 0.00) | |
| Asia | 405 | 3 | 0.7 | 413 | 1 | 0.2 | 0.3426 | 0.41 | (0.06, 2.74) | 0.41 | (0.06, 2.77) | -0.01 | (-0.02, 0.01) | |
| Other | 171 | 2 | 1.2 | 180 | 3 | 1.7 | 0.7439 | 1.31 | (0.26, 6.55) | 1.31 | (0.26, 6.77) | 0.00 | (-0.02, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4235 |
| Diabetic | 1739 | 20 | 1.2 | 1779 | 12 | 0.7 | 0.1350 | 0.58 | (0.29, 1.19) | 0.58 | (0.28, 1.19) | 0.00 | (-0.01, 0.00) | |
| Non-Diabetic | 1536 | 10 | 0.7 | 1551 | 3 | 0.2 | 0.0580 | 0.33 | (0.10, 1.10) | 0.33 | (0.10, 1.10) | 0.00 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5898 |
| <30 | 1975 | 16 | 0.8 | 1930 | 9 | 0.5 | 0.1736 | 0.57 | (0.25, 1.29) | 0.57 | (0.25, 1.29) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1300 | 14 | 1.1 | 1400 | 6 | 0.4 | 0.0535 | 0.40 | (0.16, 1.05) | 0.40 | (0.15, 1.05) | -0.01 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0186 |
| <130 | 1684 | 20 | 1.2 | 1687 | 4 | 0.2 | 0.0012 | 0.22 | (0.08, 0.60) | 0.21 | (0.08, 0.60) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1591 | 10 | 0.6 | 1643 | 11 | 0.7 | 0.8790 | 1.07 | (0.46, 2.51) | 1.07 | (0.45, 2.52) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

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User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9692 |
| <75 | 1653 | 17 | 1.0 | 1612 | 8 | 0.5 | 0.0855 | 0.49 | (0.22, 1.12) | 0.49 | (0.22, 1.12) | -0.01 | (-0.01, 0.00) | |
| 75 to <85 | 1005 | 8 | 0.8 | 1085 | 4 | 0.4 | 0.1992 | 0.47 | (0.14, 1.54) | 0.46 | (0.14, 1.54) | 0.00 | (-0.01, 0.00) | |
| >=85 | 617 | 5 | 0.8 | 633 | 3 | 0.5 | 0.4586 | 0.59 | (0.14, 2.45) | 0.58 | (0.14, 2.46) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7493 |
| <30 | 250 | 4 | 1.6 | 263 | 3 | 1.1 | 0.7664 | 0.81 | (0.20, 3.24) | 0.81 | (0.20, 3.32) | 0.00 | (-0.02, 0.02) | |
| 30 to <45 | 898 | 16 | 1.8 | 909 | 7 | 0.8 | 0.0544 | 0.43 | (0.18, 1.04) | 0.43 | (0.17, 1.04) | -0.01 | (-0.02, 0.00) | |
| >=45 | 2126 | 10 | 0.5 | 2158 | 5 | 0.2 | 0.1840 | 0.49 | (0.17, 1.44) | 0.49 | (0.17, 1.43) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3720 |
| Normal (<30) | 1216 | 14 | 1.2 | 1243 | 5 | 0.4 | 0.0338 | 0.35 | (0.13, 0.97) | 0.35 | (0.12, 0.96) | -0.01 | (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 10 | 0.6 | 1546 | 4 | 0.3 | 0.1211 | 0.43 | (0.14, 1.29) | 0.43 | (0.14, 1.29) | 0.00 | (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 500 | 6 | 1.2 | 525 | 6 | 1.1 | 0.9526 | 0.97 | (0.33, 2.85) | 0.97 | (0.32, 2.90) | 0.00 | (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2491 |
| Low, moderate or high | 2430 | 17 | 0.7 | 2495 | 6 | 0.2 | 0.0176 | 0.34 | (0.13, 0.87) | 0.34 | (0.13, 0.86) | 0.00 | (-0.01, 0.00) | |
| Very high | 834 | 13 | 1.6 | 820 | 9 | 1.1 | 0.4300 | 0.71 | (0.31, 1.65) | 0.71 | (0.30, 1.67) | 0.00 | (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5512 |
| No | 572 | 4 | 0.7 | 578 | 3 | 0.5 | 0.6946 | 0.74 | (0.17, 3.31) | 0.74 | (0.16, 3.33) | 0.00 | (-0.01, 0.01) | |
| Yes | 2703 | 26 | 1.0 | 2752 | 12 | 0.4 | 0.0187 | 0.45 | (0.23, 0.89) | 0.45 | (0.23, 0.89) | -0.01 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6638 |
| No | 344 | 3 | 0.9 | 349 | 2 | 0.6 | 0.6488 | 0.69 | (0.14, 3.42) | 0.69 | (0.14, 3.49) | 0.00 | (-0.02, 0.01) | |
| Yes | 2931 | 27 | 0.9 | 2981 | 13 | 0.4 | 0.0220 | 0.47 | (0.24, 0.91) | 0.47 | (0.24, 0.91) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 2 Proportion of patients with serious adverse events of special interest and serious other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6093 |
| No | 275 | 1 | 0.4 | 307 | 1 | 0.3 | 0.9113 | 0.88 | (0.09, 8.39) | 0.88 | (0.09, 8.51) | 0.00 | (-0.01, 0.01) | |
| Yes | 3000 | 29 | 1.0 | 3023 | 14 | 0.5 | 0.0198 | 0.48 | (0.25, 0.90) | 0.47 | (0.25, 0.90) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 21 | 0.6 | 3330 | 20 | 0.6 | 0.8324 | 0.94 | (0.51, 1.72) | 0.94 | (0.51, 1.73) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.2622 |
| 1245.110 | 2001 | 15 | 0.7 | 2052 | 11 | 0.5 | 0.3946 | 0.72 | (0.33, 1.55) | 0.71 | (0.33, 1.56) | 0.00 | (-0.01, 0.00) | |
| 1245.121 | 1274 | 6 | 0.5 | 1278 | 9 | 0.7 | 0.4409 | 1.50 | (0.53, 4.19) | 1.50 | (0.53, 4.22) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.2646 |
| Male | 2023 | 16 | 0.8 | 2068 | 18 | 0.9 | 0.7817 | 1.10 | (0.56, 2.15) | 1.10 | (0.56, 2.16) | 0.00 | ( 0.00, 0.01) | |
| Female | 1252 | 5 | 0.4 | 1262 | 2 | 0.2 | 0.2585 | 0.40 | (0.08, 2.06) | 0.40 | (0.08, 2.07) | 0.00 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.5212 |
| <65 | 766 | 8 | 1.0 | 705 | 9 | 1.3 | 0.6883 | 1.21 | (0.47, 3.12) | 1.22 | (0.47, 3.17) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 13 | 0.5 | 2625 | 11 | 0.4 | 0.6030 | 0.81 | (0.36, 1.80) | 0.81 | (0.36, 1.81) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | 0.9769 |
| North America | 434 | 5 | 1.2 | 432 | 5 | 1.2 | 0.9968 | 1.00 | (0.29, 3.44) | 1.00 | (0.29, 3.49) | 0.00 | (-0.01, 0.01) | |
| Latin America | 931 | 5 | 0.5 | 944 | 6 | 0.6 | 0.7867 | 1.18 | (0.36, 3.87) | 1.18 | (0.36, 3.89) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 9 | 0.7 | 1361 | 8 | 0.6 | 0.7797 | 0.87 | (0.34, 2.25) | 0.87 | (0.34, 2.27) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 1 | 0.2 | 413 | 0 | 0 | 0.5461 | 0.49 | (0.05, 5.26) | 0.49 | (0.04, 5.34) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 1 | 0.6 | 180 | 1 | 0.6 | 0.9704 | 0.96 | (0.10, 9.11) | 0.96 | (0.10, 9.30) | 0.00 | (-0.02, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6870 |
| Diabetic | 1739 | 18 | 1.0 | 1779 | 18 | 1.0 | 0.9430 | 0.98 | (0.51, 1.87) | 0.98 | (0.51, 1.88) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 1536 | 3 | 0.2 | 1551 | 2 | 0.1 | 0.6470 | 0.66 | (0.11, 3.94) | 0.66 | (0.11, 3.95) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7788 |
| <30 | 1975 | 8 | 0.4 | 1930 | 8 | 0.4 | 0.9568 | 1.03 | (0.39, 2.71) | 1.03 | (0.39, 2.73) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1300 | 13 | 1.0 | 1400 | 12 | 0.9 | 0.7031 | 0.86 | (0.39, 1.87) | 0.86 | (0.39, 1.89) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9031 |
| <130 | 1684 | 10 | 0.6 | 1687 | 9 | 0.5 | 0.8123 | 0.90 | (0.37, 2.20) | 0.90 | (0.36, 2.21) | 0.00 | (-0.01, 0.00) | |
| >=130 | 1591 | 11 | 0.7 | 1643 | 11 | 0.7 | 0.9392 | 0.97 | (0.42, 2.23) | 0.97 | (0.42, 2.24) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3599 |
| <75 | 1653 | 9 | 0.5 | 1612 | 12 | 0.7 | 0.4787 | 1.36 | (0.58, 3.21) | 1.36 | (0.57, 3.24) | 0.00 | ( 0.00, 0.01) | |
| 75 to <85 | 1005 | 8 | 0.8 | 1085 | 4 | 0.4 | 0.1992 | 0.47 | (0.14, 1.54) | 0.46 | (0.14, 1.54) | 0.00 | (-0.01, 0.00) | |
| >=85 | 617 | 4 | 0.6 | 633 | 4 | 0.6 | 0.9606 | 0.97 | (0.24, 3.83) | 0.97 | (0.24, 3.88) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4200 |
| <30 | 250 | 1 | 0.4 | 263 | 4 | 1.5 | 0.2305 | 2.92 | (0.47,18.25) | 2.95 | (0.46,18.89) | 0.01 | (-0.01, 0.03) | |
| 30 to <45 | 898 | 5 | 0.6 | 909 | 4 | 0.4 | 0.7311 | 0.80 | (0.22, 2.94) | 0.79 | (0.21, 2.96) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 15 | 0.7 | 2158 | 12 | 0.6 | 0.5309 | 0.79 | (0.37, 1.67) | 0.78 | (0.37, 1.68) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2201 |
| Normal (<30) | 1216 | 2 | 0.2 | 1243 | 6 | 0.5 | 0.1920 | 2.54 | (0.59,10.89) | 2.55 | (0.59,10.97) | 0.00 | ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 7 | 0.5 | 1546 | 7 | 0.5 | 0.9959 | 1.00 | (0.35, 2.85) | 1.00 | (0.35, 2.87) | 0.00 | ( 0.00, 0.00) | |
| Macroalbuminuria (>300) | 500 | 12 | 2.4 | 525 | 7 | 1.3 | 0.2098 | 0.56 | (0.22, 1.41) | 0.55 | (0.22, 1.41) | -0.01 | (-0.03, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4316 |
| Low, moderate or high | 2430 | 12 | 0.5 | 2495 | 14 | 0.6 | 0.7487 | 1.13 | (0.53, 2.44) | 1.13 | (0.52, 2.45) | 0.00 | ( 0.00, 0.00) | |
| Very high | 834 | 9 | 1.1 | 820 | 6 | 0.7 | 0.4551 | 0.68 | (0.24, 1.89) | 0.68 | (0.24, 1.90) | 0.00 | (-0.01, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4530 |
| No | 572 | 4 | 0.7 | 578 | 2 | 0.3 | 0.4354 | 0.55 | (0.12, 2.54) | 0.55 | (0.12, 2.56) | 0.00 | (-0.01, 0.01) | |
| Yes | 2703 | 17 | 0.6 | 2752 | 18 | 0.7 | 0.9104 | 1.04 | (0.54, 2.01) | 1.04 | (0.53, 2.02) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6878 |
| No | 344 | 3 | 0.9 | 349 | 2 | 0.6 | 0.6488 | 0.68 | (0.13, 3.55) | 0.68 | (0.13, 3.53) | 0.00 | (-0.02, 0.01) | |
| Yes | 2931 | 18 | 0.6 | 2981 | 18 | 0.6 | 0.9576 | 0.98 | (0.51, 1.88) | 0.98 | (0.51, 1.89) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events leading to lower limb amputation (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5190 |
| No | 275 | 1 | 0.4 | 307 | 0 | 0 | 0.4899 | 0.44 | (0.04, 4.88) | 0.44 | (0.04, 4.88) | 0.00 | (-0.02, 0.01) | |
| Yes | 3000 | 20 | 0.7 | 3023 | 20 | 0.7 | 0.9789 | 0.99 | (0.53, 1.84) | 0.99 | (0.53, 1.85) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 24 | 0.7 | 3330 | 22 | 0.7 | 0.7222 | 0.90 | (0.51, 1.60) | 0.90 | (0.50, 1.61) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.3239 |
| 1245.110 | 2001 | 14 | 0.7 | 2052 | 16 | 0.8 | 0.7662 | 1.11 | (0.55, 2.28) | 1.12 | (0.54, 2.29) | 0.00 | ( 0.00, 0.01) | |
| 1245.121 | 1274 | 10 | 0.8 | 1278 | 6 | 0.5 | 0.3129 | 0.60 | (0.22, 1.64) | 0.60 | (0.22, 1.65) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.3750 |
| Male | 2023 | 18 | 0.9 | 2068 | 19 | 0.9 | 0.9239 | 1.03 | (0.54, 1.96) | 1.03 | (0.54, 1.97) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 6 | 0.5 | 1262 | 3 | 0.2 | 0.3384 | 0.53 | (0.15, 1.97) | 0.53 | (0.14, 1.97) | 0.00 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.4824 |
| <65 | 766 | 3 | 0.4 | 705 | 1 | 0.1 | 0.4229 | 0.46 | (0.07, 3.17) | 0.46 | (0.07, 3.16) | 0.00 | (-0.01, 0.00) | |
| >=65 | 2509 | 21 | 0.8 | 2625 | 21 | 0.8 | 0.8832 | 0.96 | (0.52, 1.75) | 0.96 | (0.52, 1.75) | 0.00 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.3632 |
| North America | 434 | 4 | 0.9 | 432 | 3 | 0.7 | 0.7277 | 0.78 | (0.19, 3.15) | 0.78 | (0.19, 3.17) | 0.00 | (-0.01, 0.01) | |
| Latin America | 931 | 5 | 0.5 | 944 | 9 | 1.0 | 0.2899 | 1.78 | (0.60, 5.26) | 1.79 | (0.60, 5.33) | 0.00 | ( 0.00, 0.01) | |
| Europe | 1334 | 11 | 0.8 | 1361 | 5 | 0.4 | 0.1241 | 0.45 | (0.16, 1.28) | 0.45 | (0.15, 1.28) | 0.00 | (-0.01, 0.00) | |
| Asia | 405 | 4 | 1.0 | 413 | 3 | 0.7 | 0.6696 | 0.72 | (0.16, 3.20) | 0.72 | (0.16, 3.24) | 0.00 | (-0.02, 0.01) | |
| Other | 171 | 0 | 0 | 180 | 2 | 1.1 | 0.3429 | 2.87 | (0.29,28.17) | 2.90 | (0.29,28.55) | 0.01 | (-0.01, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5279 |
| Diabetic | 1739 | 13 | 0.7 | 1779 | 14 | 0.8 | 0.8950 | 1.05 | (0.50, 2.23) | 1.05 | (0.49, 2.25) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 1536 | 11 | 0.7 | 1551 | 8 | 0.5 | 0.4755 | 0.72 | (0.29, 1.78) | 0.72 | (0.29, 1.79) | 0.00 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1853 |
| <30 | 1975 | 19 | 1.0 | 1930 | 13 | 0.7 | 0.3112 | 0.70 | (0.34, 1.41) | 0.69 | (0.34, 1.41) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1300 | 5 | 0.4 | 1400 | 9 | 0.6 | 0.3488 | 1.68 | (0.56, 5.01) | 1.68 | (0.56, 5.04) | 0.00 | ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6116 |
| <130 | 1684 | 15 | 0.9 | 1687 | 12 | 0.7 | 0.5494 | 0.79 | (0.37, 1.69) | 0.79 | (0.37, 1.70) | 0.00 | (-0.01, 0.00) | |
| >=130 | 1591 | 9 | 0.6 | 1643 | 10 | 0.6 | 0.8728 | 1.08 | (0.44, 2.64) | 1.08 | (0.44, 2.65) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7590 |
| <75 | 1653 | 15 | 0.9 | 1612 | 14 | 0.9 | 0.8915 | 0.95 | (0.46, 1.96) | 0.95 | (0.46, 1.98) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 6 | 0.6 | 1085 | 4 | 0.4 | 0.4638 | 0.64 | (0.19, 2.12) | 0.64 | (0.19, 2.13) | 0.00 | (-0.01, 0.00) | |
| >=85 | 617 | 3 | 0.5 | 633 | 4 | 0.6 | 0.7375 | 1.29 | (0.29, 5.72) | 1.29 | (0.29, 5.80) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6584 |
| <30 | 250 | 3 | 1.2 | 263 | 3 | 1.1 | 0.9872 | 0.99 | (0.24, 4.14) | 0.99 | (0.23, 4.31) | 0.00 | (-0.02, 0.02) | |
| 30 to <45 | 898 | 5 | 0.6 | 909 | 7 | 0.8 | 0.5756 | 1.38 | (0.44, 4.33) | 1.39 | (0.44, 4.37) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 16 | 0.8 | 2158 | 12 | 0.6 | 0.4221 | 0.74 | (0.35, 1.56) | 0.74 | (0.35, 1.56) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3584 |
| Normal (<30) | 1216 | 7 | 0.6 | 1243 | 3 | 0.2 | 0.1933 | 0.42 | (0.11, 1.62) | 0.42 | (0.11, 1.62) | 0.00 | (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 14 | 0.9 | 1546 | 17 | 1.1 | 0.5929 | 1.21 | (0.60, 2.45) | 1.21 | (0.60, 2.47) | 0.00 | (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 500 | 3 | 0.6 | 525 | 2 | 0.4 | 0.6144 | 0.63 | (0.11, 3.79) | 0.63 | (0.10, 3.81) | 0.00 | (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3557 |
| Low, moderate or high | 2430 | 16 | 0.7 | 2495 | 12 | 0.5 | 0.4053 | 0.73 | (0.34, 1.54) | 0.73 | (0.34, 1.54) | 0.00 | (-0.01, 0.00) | |
| Very high | 834 | 8 | 1.0 | 820 | 10 | 1.2 | 0.6038 | 1.28 | (0.51, 3.23) | 1.28 | (0.50, 3.27) | 0.00 | (-0.01, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1685 |
| No | 572 | 9 | 1.6 | 578 | 4 | 0.7 | 0.1747 | 0.47 | (0.15, 1.43) | 0.47 | (0.15, 1.44) | -0.01 | (-0.02, 0.00) | |
| Yes | 2703 | 15 | 0.6 | 2752 | 18 | 0.7 | 0.6357 | 1.18 | (0.60, 2.34) | 1.18 | (0.59, 2.35) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4099 |
| No | 344 | 7 | 2.0 | 349 | 4 | 1.1 | 0.3737 | 0.60 | (0.19, 1.89) | 0.59 | (0.18, 1.91) | -0.01 | (-0.03, 0.01) | |
| Yes | 2931 | 17 | 0.6 | 2981 | 18 | 0.6 | 0.9033 | 1.04 | (0.54, 2.02) | 1.04 | (0.54, 2.03) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hepatic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.1843 |
| No | 275 | 3 | 1.1 | 307 | 0 | 0 | 0.1407 | 0.22 | (0.02, 2.01) | 0.22 | (0.02, 1.99) | -0.01 | (-0.03, 0.00) | |
| Yes | 3000 | 21 | 0.7 | 3023 | 22 | 0.7 | 0.9003 | 1.04 | (0.57, 1.89) | 1.04 | (0.57, 1.89) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 3 | 0.1 | 3330 | 3 | 0.1 | 0.9801 | 0.98 (0.22, 4.32) | 0.98 (0.22, 4.33) | 0.00 ( 0.00, 0.00) | |
| Study | | | | | | | | | | | |
| 1245.110 | 2001 | 2 | 0.1 | 2052 | 3 | 0.1 | | | | | |
| 1245.121 | 1274 | 1 | 0.1 | 1278 | 0 | 0 | | | | | |
| Sex | | | | | | | | | | | |
| Male | 2023 | 2 | 0.1 | 2068 | 1 | <0.1 | | | | | |
| Female | 1252 | 1 | 0.1 | 1262 | 2 | 0.2 | | | | | |
| Age [years] | | | | | | | | | | | |
| <65 | 766 | 3 | 0.4 | 705 | 0 | 0 | | | | | |
| >=65 | 2509 | 0 | 0 | 2625 | 3 | 0.1 | | | | | |
| Region | | | | | | | | | | | |
| North America | 434 | 1 | 0.2 | 432 | 1 | 0.2 | | | | | |
| Latin America | 931 | 0 | 0 | 944 | 0 | 0 | | | | | |
| Europe | 1334 | 0 | 0 | 1361 | 1 | 0.1 | | | | | |
| Asia | 405 | 1 | 0.2 | 413 | 0 | 0 | | | | | |
| Other | 171 | 1 | 0.6 | 180 | 1 | 0.6 | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | |
| Diabetic | 1739 | 3 | 0.2 | 1779 | 3 | 0.2 | | | | | |
| Non-Diabetic | 1536 | 0 | 0 | 1551 | 0 | 0 | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | |
| <30 | 1975 | 2 | 0.1 | 1930 | 1 | 0.1 | | | | | |
| >=30 | 1300 | 1 | 0.1 | 1400 | 2 | 0.1 | | | | | |
| Baseline SBP [mmHg] | | | | | | | | | | | |
| <130 | 1684 | 1 | 0.1 | 1687 | 0 | 0 | | | | | |
| >=130 | 1591 | 2 | 0.1 | 1643 | 3 | 0.2 | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | |
| <75 | 1653 | 0 | 0 | 1612 | 1 | 0.1 | | | | | |
| 75 to <85 | 1005 | 2 | 0.2 | 1085 | 2 | 0.2 | | | | | |
| >=85 | 617 | 1 | 0.2 | 633 | 0 | 0 | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | |
| <30 | 250 | 1 | 0.4 | 263 | 1 | 0.4 | | | | | |
| 30 to <45 | 898 | 0 | 0 | 909 | 1 | 0.1 | | | | | |
| >=45 | 2126 | 2 | 0.1 | 2158 | 1 | <0.1 | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | |
| Normal (<30) | 1216 | 0 | 0 | 1243 | 0 | 0 | | | | | |
| Microalbuminuria (30 to <=300) | 1548 | 2 | 0.1 | 1546 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 500 | 1 | 0.2 | 525 | 3 | 0.6 | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | |
| Low, moderate or high | 2430 | 2 | 0.1 | 2495 | 1 | <0.1 | | | | | |
| Very high | 834 | 1 | 0.1 | 820 | 2 | 0.2 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | |
| No | 572 | 1 | 0.2 | 578 | 0 | 0 | | | | | |
| Yes | 2703 | 2 | 0.1 | 2752 | 3 | 0.1 | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | |
| No | 344 | 0 | 0 | 349 | 0 | 0 | | | | | |
| Yes | 2931 | 3 | 0.1 | 2981 | 3 | 0.1 | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Events indicative of ketoacidosis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | |
| No | 275 | 1 | 0.4 | 307 | 1 | 0.3 | | | | | |
| Yes | 3000 | 2 | 0.1 | 3023 | 2 | 0.1 | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 13 | 0.4 | 3330 | 14 | 0.4 | 0.8769 | 1.06 | (0.50, 2.26) | 1.06 | (0.50, 2.26) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.5874 |
| 1245.110 | 2001 | 6 | 0.3 | 2052 | 8 | 0.4 | 0.6254 | 1.30 | (0.45, 3.74) | 1.30 | (0.45, 3.76) | 0.00 | ( 0.00, 0.00) | |
| 1245.121 | 1274 | 7 | 0.5 | 1278 | 6 | 0.5 | 0.7767 | 0.85 | (0.29, 2.54) | 0.85 | (0.29, 2.55) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0323 |
| Male | 2023 | 11 | 0.5 | 2068 | 6 | 0.3 | 0.2082 | 0.53 | (0.20, 1.44) | 0.53 | (0.20, 1.44) | 0.00 | (-0.01, 0.00) | |
| Female | 1252 | 2 | 0.2 | 1262 | 8 | 0.6 | 0.0583 | 4.00 | (0.85,18.93) | 4.02 | (0.85,19.04) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6906 |
| <65 | 766 | 4 | 0.5 | 705 | 3 | 0.4 | 0.7954 | 0.82 | (0.18, 3.66) | 0.82 | (0.18, 3.68) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 9 | 0.4 | 2625 | 11 | 0.4 | 0.7302 | 1.17 | (0.48, 2.81) | 1.17 | (0.48, 2.82) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | 0.9647 |
| North America | 434 | 2 | 0.5 | 432 | 3 | 0.7 | 0.6746 | 1.41 | (0.28, 7.11) | 1.42 | (0.28, 7.24) | 0.00 | (-0.01, 0.01) | |
| Latin America | 931 | 5 | 0.5 | 944 | 5 | 0.5 | 0.9717 | 0.98 | (0.28, 3.37) | 0.98 | (0.28, 3.39) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 3 | 0.2 | 1361 | 4 | 0.3 | 0.7272 | 1.30 | (0.29, 5.82) | 1.31 | (0.29, 5.85) | 0.00 | ( 0.00, 0.00) | |
| Asia | 405 | 1 | 0.2 | 413 | 1 | 0.2 | 0.9928 | 0.99 | (0.14, 7.22) | 0.99 | (0.14, 7.17) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 2 | 1.2 | 180 | 1 | 0.6 | 0.5769 | 0.57 | (0.08, 4.21) | 0.57 | (0.07, 4.30) | -0.01 | (-0.03, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5846 |
| Diabetic | 1739 | 13 | 0.7 | 1779 | 13 | 0.7 | 0.9596 | 0.98 | (0.46, 2.11) | 0.98 | (0.45, 2.12) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 1536 | 0 | 0 | 1551 | 1 | 0.1 | 0.5697 | 1.98 | (0.18,21.87) | 1.98 | (0.18,21.90) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1184 |
| <30 | 1975 | 7 | 0.4 | 1930 | 3 | 0.2 | 0.2251 | 0.44 | (0.11, 1.72) | 0.44 | (0.11, 1.71) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1300 | 6 | 0.5 | 1400 | 11 | 0.8 | 0.2964 | 1.69 | (0.62, 4.56) | 1.69 | (0.62, 4.60) | 0.00 | ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9025 |
| <130 | 1684 | 6 | 0.4 | 1687 | 6 | 0.4 | 0.9974 | 1.00 | (0.32, 3.09) | 1.00 | (0.32, 3.10) | 0.00 | ( 0.00, 0.00) | |
| >=130 | 1591 | 7 | 0.4 | 1643 | 8 | 0.5 | 0.8570 | 1.10 | (0.40, 3.01) | 1.10 | (0.40, 3.03) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
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Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4498 |
| <75 | 1653 | 8 | 0.5 | 1612 | 5 | 0.3 | 0.4371 | 0.64 | (0.21, 1.97) | 0.64 | (0.21, 1.97) | 0.00 | (-0.01, 0.00) | |
| 75 to <85 | 1005 | 4 | 0.4 | 1085 | 8 | 0.7 | 0.3066 | 1.85 | (0.56, 6.14) | 1.86 | (0.56, 6.19) | 0.00 | ( 0.00, 0.01) | |
| >=85 | 617 | 1 | 0.2 | 633 | 1 | 0.2 | 0.9755 | 0.97 | (0.14, 6.81) | 0.97 | (0.14, 6.88) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.2638 |
| <30 | 250 | 1 | 0.4 | 263 | 5 | 1.9 | 0.1484 | 3.49 | (0.57,21.32) | 3.54 | (0.57,21.93) | 0.01 | ( 0.00, 0.03) | |
| 30 to <45 | 898 | 5 | 0.6 | 909 | 5 | 0.6 | 0.9939 | 1.00 | (0.29, 3.44) | 1.00 | (0.29, 3.46) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 7 | 0.3 | 2158 | 4 | 0.2 | 0.3558 | 0.57 | (0.17, 1.93) | 0.56 | (0.17, 1.93) | 0.00 | ( 0.00, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6501 |
| Normal (<30) | 1216 | 4 | 0.3 | 1243 | 5 | 0.4 | 0.7590 | 1.23 | (0.33, 4.57) | 1.23 | (0.33, 4.59) | 0.00 | ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 5 | 0.3 | 1546 | 3 | 0.2 | 0.4791 | 0.60 | (0.14, 2.51) | 0.60 | (0.14, 2.51) | 0.00 | ( 0.00, 0.00) | |
| Macroalbuminuria (>300) | 500 | 4 | 0.8 | 525 | 6 | 1.1 | 0.5854 | 1.42 | (0.40, 4.99) | 1.42 | (0.40, 5.07) | 0.00 | (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3109 |
| Low, moderate or high | 2430 | 8 | 0.3 | 2495 | 6 | 0.2 | 0.5760 | 0.74 | (0.26, 2.14) | 0.74 | (0.26, 2.14) | 0.00 | ( 0.00, 0.00) | |
| Very high | 834 | 5 | 0.6 | 820 | 8 | 1.0 | 0.3805 | 1.64 | (0.54, 5.01) | 1.65 | (0.54, 5.06) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1189 |
| No | 572 | 1 | 0.2 | 578 | 5 | 0.9 | 0.1332 | 3.63 | (0.60,21.95) | 3.65 | (0.60,22.28) | 0.01 | ( 0.00, 0.02) | |
| Yes | 2703 | 12 | 0.4 | 2752 | 9 | 0.3 | 0.4939 | 0.74 | (0.31, 1.76) | 0.74 | (0.31, 1.76) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9025 |
| No | 344 | 1 | 0.3 | 349 | 1 | 0.3 | 0.9483 | 0.94 | (0.14, 6.35) | 0.94 | (0.13, 6.57) | 0.00 | (-0.01, 0.01) | |
| Yes | 2931 | 12 | 0.4 | 2981 | 13 | 0.4 | 0.8692 | 1.07 | (0.49, 2.34) | 1.07 | (0.49, 2.35) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypoglycaemic events (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8820 |
| No | 275 | 0 | 0 | 307 | 0 | 0 | 0.9161 | 0.86 | (0.05,13.65) | 0.86 | (0.05,13.88) | 0.00 | (-0.01, 0.01) | |
| Yes | 3000 | 13 | 0.4 | 3023 | 14 | 0.5 | 0.8592 | 1.07 | (0.50, 2.27) | 1.07 | (0.50, 2.28) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 28 | 0.9 | 3330 | 36 | 1.1 | 0.3544 | 1.26 | (0.77, 2.06) | 1.26 | (0.77, 2.08) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.2624 |
| 1245.110 | 2001 | 19 | 0.9 | 2052 | 29 | 1.4 | 0.1725 | 1.49 | (0.84, 2.65) | 1.50 | (0.84, 2.68) | 0.00 | ( 0.00, 0.01) | |
| 1245.121 | 1274 | 9 | 0.7 | 1278 | 7 | 0.5 | 0.6116 | 0.78 | (0.29, 2.08) | 0.77 | (0.29, 2.08) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0811 |
| Male | 2023 | 20 | 1.0 | 2068 | 18 | 0.9 | 0.6899 | 0.88 | (0.47, 1.66) | 0.88 | (0.46, 1.67) | 0.00 | (-0.01, 0.00) | |
| Female | 1252 | 8 | 0.6 | 1262 | 18 | 1.4 | 0.0522 | 2.23 | (0.97, 5.11) | 2.24 | (0.97, 5.18) | 0.01 | ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.6659 |
| <65 | 766 | 4 | 0.5 | 705 | 6 | 0.9 | 0.4508 | 1.62 | (0.46, 5.72) | 1.62 | (0.46, 5.79) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 24 | 1.0 | 2625 | 30 | 1.1 | 0.5092 | 1.20 | (0.70, 2.04) | 1.20 | (0.70, 2.06) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.8333 |
| North America | 434 | 5 | 1.2 | 432 | 8 | 1.9 | 0.4166 | 1.55 | (0.53, 4.49) | 1.56 | (0.53, 4.61) | 0.01 | (-0.01, 0.02) | |
| Latin America | 931 | 8 | 0.9 | 944 | 13 | 1.4 | 0.2728 | 1.62 | (0.68, 3.88) | 1.63 | (0.67, 3.95) | 0.01 | ( 0.00, 0.01) | |
| Europe | 1334 | 12 | 0.9 | 1361 | 12 | 0.9 | 0.9627 | 0.98 | (0.44, 2.17) | 0.98 | (0.44, 2.19) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 1 | 0.2 | 413 | 0 | 0 | 0.5461 | 0.49 | (0.05, 5.26) | 0.49 | (0.04, 5.34) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 2 | 1.2 | 180 | 3 | 1.7 | 0.7202 | 1.35 | (0.26, 6.95) | 1.35 | (0.26, 7.04) | 0.00 | (-0.02, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7241 |
| Diabetic | 1739 | 15 | 0.9 | 1779 | 21 | 1.2 | 0.3552 | 1.36 | (0.70, 2.64) | 1.37 | (0.70, 2.66) | 0.00 | ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 13 | 0.8 | 1551 | 15 | 1.0 | 0.7273 | 1.14 | (0.54, 2.39) | 1.14 | (0.54, 2.41) | 0.00 | (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2821 |
| <30 | 1975 | 16 | 0.8 | 1930 | 15 | 0.8 | 0.8896 | 0.95 | (0.47, 1.92) | 0.95 | (0.47, 1.93) | 0.00 | (-0.01, 0.01) | |
| >=30 | 1300 | 12 | 0.9 | 1400 | 21 | 1.5 | 0.1626 | 1.64 | (0.81, 3.32) | 1.65 | (0.81, 3.37) | 0.01 | ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4160 |
| <130 | 1684 | 16 | 1.0 | 1687 | 24 | 1.4 | 0.2217 | 1.48 | (0.79, 2.77) | 1.49 | (0.79, 2.81) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 1591 | 12 | 0.8 | 1643 | 12 | 0.7 | 0.9383 | 0.97 | (0.44, 2.15) | 0.97 | (0.43, 2.16) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5535 |
| <75 | 1653 | 18 | 1.1 | 1612 | 19 | 1.2 | 0.8224 | 1.08 | (0.57, 2.05) | 1.08 | (0.56, 2.06) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 6 | 0.6 | 1085 | 13 | 1.2 | 0.1584 | 1.93 | (0.76, 4.91) | 1.95 | (0.76, 4.99) | 0.01 | ( 0.00, 0.01) | |
| >=85 | 617 | 4 | 0.6 | 633 | 4 | 0.6 | 0.9739 | 0.98 | (0.27, 3.59) | 0.98 | (0.26, 3.63) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4535 |
| <30 | 250 | 6 | 2.4 | 263 | 5 | 1.9 | 0.7495 | 0.82 | (0.25, 2.72) | 0.82 | (0.24, 2.75) | 0.00 | (-0.03, 0.02) | |
| 30 to <45 | 898 | 9 | 1.0 | 909 | 17 | 1.9 | 0.1258 | 1.85 | (0.83, 4.14) | 1.87 | (0.83, 4.22) | 0.01 | ( 0.00, 0.02) | |
| >=45 | 2126 | 13 | 0.6 | 2158 | 14 | 0.6 | 0.8842 | 1.06 | (0.50, 2.25) | 1.06 | (0.50, 2.26) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2049 |
| Normal (<30) | 1216 | 8 | 0.7 | 1243 | 16 | 1.3 | 0.1139 | 1.95 | (0.84, 4.55) | 1.97 | (0.84, 4.61) | 0.01 | ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 16 | 1.0 | 1546 | 13 | 0.8 | 0.5637 | 0.81 | (0.39, 1.67) | 0.81 | (0.39, 1.68) | 0.00 | (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 500 | 3 | 0.6 | 525 | 7 | 1.3 | 0.2247 | 2.25 | (0.59, 8.59) | 2.26 | (0.58, 8.78) | 0.01 | ( 0.00, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.6168 |
| Low, moderate or high | 2430 | 17 | 0.7 | 2495 | 21 | 0.8 | 0.5796 | 1.20 | (0.63, 2.27) | 1.20 | (0.63, 2.28) | 0.00 | ( 0.00, 0.01) | |
| Very high | 834 | 10 | 1.2 | 820 | 15 | 1.8 | 0.2728 | 1.55 | (0.70, 3.43) | 1.56 | (0.70, 3.51) | 0.01 | (-0.01, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2109 |
| No | 572 | 4 | 0.7 | 578 | 10 | 1.7 | 0.1205 | 2.32 | (0.78, 6.93) | 2.34 | (0.77, 7.09) | 0.01 | ( 0.00, 0.02) | |
| Yes | 2703 | 24 | 0.9 | 2752 | 26 | 0.9 | 0.8360 | 1.06 | (0.61, 1.84) | 1.06 | (0.61, 1.85) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7456 |
| No | 344 | 3 | 0.9 | 349 | 5 | 1.4 | 0.5208 | 1.53 | (0.41, 5.71) | 1.54 | (0.40, 5.87) | 0.01 | (-0.01, 0.02) | |
| Yes | 2931 | 25 | 0.9 | 2981 | 31 | 1.0 | 0.4699 | 1.21 | (0.72, 2.05) | 1.22 | (0.72, 2.06) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.3886 |
| No | 275 | 2 | 0.7 | 307 | 1 | 0.3 | 0.5350 | 0.53 | (0.07, 4.03) | 0.53 | (0.07, 4.05) | 0.00 | (-0.02, 0.01) | |
| Yes | 3000 | 26 | 0.9 | 3023 | 35 | 1.2 | 0.2645 | 1.33 | (0.80, 2.21) | 1.34 | (0.80, 2.23) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall^ | 3275 | 2 | 0.1 | 3330 | 1 | <0.1 | | | | | |
| Study^ | | | | | | | | | | | |
| 1245.110 | 2001 | 2 | 0.1 | 2052 | 1 | <0.1 | | | | | |
| 1245.121 | 1274 | 0 | 0 | 1278 | 0 | 0 | | | | | |
| Sex^ | | | | | | | | | | | |
| Male | 2023 | 2 | 0.1 | 2068 | 1 | <0.1 | | | | | |
| Female | 1252 | 0 | 0 | 1262 | 0 | 0 | | | | | |
| Age [years]^ | | | | | | | | | | | |
| <65 | 766 | 0 | 0 | 705 | 0 | 0 | | | | | |
| >=65 | 2509 | 2 | 0.1 | 2625 | 1 | <0.1 | | | | | |
| Region^ | | | | | | | | | | | |
| North America | 434 | 0 | 0 | 432 | 1 | 0.2 | | | | | |
| Latin America | 931 | 0 | 0 | 944 | 0 | 0 | | | | | |
| Europe | 1334 | 2 | 0.1 | 1361 | 0 | 0 | | | | | |
| Asia | 405 | 0 | 0 | 413 | 0 | 0 | | | | | |
| Other | 171 | 0 | 0 | 180 | 0 | 0 | | | | | |
| Baseline Diabetes Status^ | | | | | | | | | | | |
| Diabetic | 1739 | 1 | 0.1 | 1779 | 0 | 0 | | | | | |
| Non-Diabetic | 1536 | 1 | 0.1 | 1551 | 1 | 0.1 | | | | | |
| Baseline BMI [kg/m²]^ | | | | | | | | | | | |
| <30 | 1975 | 1 | 0.1 | 1930 | 0 | 0 | | | | | |
| >=30 | 1300 | 1 | 0.1 | 1400 | 1 | 0.1 | | | | | |
| Baseline SBP [mmHg]^ | | | | | | | | | | | |
| <130 | 1684 | 1 | 0.1 | 1687 | 1 | 0.1 | | | | | |
| >=130 | 1591 | 1 | 0.1 | 1643 | 0 | 0 | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg]^ | | | | | | | | | | | |
| <75 | 1653 | 2 | 0.1 | 1612 | 1 | 0.1 | | | | | |
| 75 to <85 | 1005 | 0 | 0 | 1085 | 0 | 0 | | | | | |
| >=85 | 617 | 0 | 0 | 633 | 0 | 0 | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²]^ | | | | | | | | | | | |
| <30 | 250 | 0 | 0 | 263 | 0 | 0 | | | | | |
| 30 to <45 | 898 | 1 | 0.1 | 909 | 0 | 0 | | | | | |
| >=45 | 2126 | 1 | <0.1 | 2158 | 1 | <0.1 | | | | | |
| Baseline UACR [mg/g]^ | | | | | | | | | | | |
| Normal (<30) | 1216 | 0 | 0 | 1243 | 1 | 0.1 | | | | | |
| Microalbuminuria (30 to <=300) | 1548 | 1 | 0.1 | 1546 | 0 | 0 | | | | | |
| Macroalbuminuria (>300) | 500 | 1 | 0.2 | 525 | 0 | 0 | | | | | |
| Baseline KDIGO risk category^ | | | | | | | | | | | |
| Low, moderate or high | 2430 | 1 | <0.1 | 2495 | 1 | <0.1 | | | | | |
| Very high | 834 | 1 | 0.1 | 820 | 0 | 0 | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi^ | | | | | | | | | | | |
| No | 572 | 1 | 0.2 | 578 | 0 | 0 | | | | | |
| Yes | 2703 | 1 | <0.1 | 2752 | 1 | <0.1 | | | | | |
| Baseline use of beta-blockers^ | | | | | | | | | | | |
| No | 344 | 0 | 0 | 349 | 0 | 0 | | | | | |
| Yes | 2931 | 2 | 0.1 | 2981 | 1 | <0.1 | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Genital infections (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics^ | | | | | | | | | | | |
| No | 275 | 0 | 0 | 307 | 0 | 0 | | | | | |
| Yes | 3000 | 2 | 0.1 | 3023 | 1 | <0.1 | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 14 | 0.4 | 3330 | 16 | 0.5 | 0.7573 | 1.12 | (0.55, 2.29) | 1.12 | (0.55, 2.30) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.8737 |
| 1245.110 | 2001 | 11 | 0.5 | 2052 | 13 | 0.6 | 0.7281 | 1.15 | (0.52, 2.57) | 1.15 | (0.52, 2.58) | 0.00 | ( 0.00, 0.01) | |
| 1245.121 | 1274 | 3 | 0.2 | 1278 | 3 | 0.2 | 0.9969 | 1.00 | (0.20, 4.93) | 1.00 | (0.20, 4.95) | 0.00 | ( 0.00, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.2550 |
| Male | 2023 | 9 | 0.4 | 2068 | 7 | 0.3 | 0.5822 | 0.76 | (0.28, 2.03) | 0.76 | (0.28, 2.04) | 0.00 | ( 0.00, 0.00) | |
| Female | 1252 | 5 | 0.4 | 1262 | 9 | 0.7 | 0.2924 | 1.78 | (0.60, 5.30) | 1.79 | (0.60, 5.35) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.9766 |
| <65 | 766 | 2 | 0.3 | 705 | 2 | 0.3 | 0.9362 | 1.08 | (0.15, 7.67) | 1.08 | (0.15, 7.71) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 12 | 0.5 | 2625 | 14 | 0.5 | 0.7761 | 1.12 | (0.52, 2.41) | 1.12 | (0.52, 2.42) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | 0.7400 |
| North America | 434 | 1 | 0.2 | 432 | 4 | 0.9 | 0.2183 | 3.01 | (0.48,19.02) | 3.03 | (0.48,19.33) | 0.01 | ( 0.00, 0.02) | |
| Latin America | 931 | 4 | 0.4 | 944 | 4 | 0.4 | 0.9900 | 0.99 | (0.25, 3.93) | 0.99 | (0.25, 3.96) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 7 | 0.5 | 1361 | 6 | 0.4 | 0.7474 | 0.84 | (0.28, 2.48) | 0.84 | (0.28, 2.49) | 0.00 | (-0.01, 0.00) | |
| Asia | 405 | 1 | 0.2 | 413 | 0 | 0 | 0.5461 | 0.49 | (0.05, 5.26) | 0.49 | (0.04, 5.34) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 1 | 0.6 | 180 | 2 | 1.1 | 0.6556 | 1.58 | (0.21,11.95) | 1.59 | (0.21,12.21) | 0.01 | (-0.02, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7483 |
| Diabetic | 1739 | 7 | 0.4 | 1779 | 9 | 0.5 | 0.6571 | 1.25 | (0.47, 3.35) | 1.25 | (0.46, 3.37) | 0.00 | ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 7 | 0.5 | 1551 | 7 | 0.5 | 0.9817 | 0.99 | (0.35, 2.81) | 0.99 | (0.35, 2.82) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3289 |
| <30 | 1975 | 8 | 0.4 | 1930 | 6 | 0.3 | 0.6019 | 0.76 | (0.26, 2.17) | 0.76 | (0.26, 2.18) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1300 | 6 | 0.5 | 1400 | 10 | 0.7 | 0.3806 | 1.56 | (0.57, 4.26) | 1.56 | (0.57, 4.31) | 0.00 | ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4824 |
| <130 | 1684 | 7 | 0.4 | 1687 | 10 | 0.6 | 0.4962 | 1.39 | (0.53, 3.65) | 1.40 | (0.53, 3.69) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 1591 | 7 | 0.4 | 1643 | 6 | 0.4 | 0.7345 | 0.83 | (0.28, 2.46) | 0.83 | (0.28, 2.47) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5245 |
| <75 | 1653 | 9 | 0.5 | 1612 | 7 | 0.4 | 0.6428 | 0.79 | (0.30, 2.12) | 0.79 | (0.29, 2.13) | 0.00 | (-0.01, 0.00) | |
| 75 to <85 | 1005 | 3 | 0.3 | 1085 | 7 | 0.6 | 0.2758 | 1.99 | (0.56, 7.07) | 2.00 | (0.56, 7.14) | 0.00 | ( 0.00, 0.01) | |
| >=85 | 617 | 2 | 0.3 | 633 | 2 | 0.3 | 0.9812 | 0.98 | (0.17, 5.63) | 0.98 | (0.17, 5.67) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8148 |
| <30 | 250 | 4 | 1.6 | 263 | 3 | 1.1 | 0.7212 | 0.77 | (0.19, 3.20) | 0.77 | (0.18, 3.20) | 0.00 | (-0.03, 0.02) | |
| 30 to <45 | 898 | 4 | 0.4 | 909 | 6 | 0.7 | 0.5696 | 1.41 | (0.43, 4.68) | 1.42 | (0.42, 4.74) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 6 | 0.3 | 2158 | 7 | 0.3 | 0.8021 | 1.15 | (0.39, 3.43) | 1.15 | (0.39, 3.43) | 0.00 | ( 0.00, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6737 |
| Normal (<30) | 1216 | 4 | 0.3 | 1243 | 7 | 0.6 | 0.3878 | 1.71 | (0.50, 5.81) | 1.71 | (0.50, 5.86) | 0.00 | ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 6 | 0.4 | 1546 | 7 | 0.5 | 0.8000 | 1.14 | (0.40, 3.25) | 1.15 | (0.40, 3.28) | 0.00 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 500 | 3 | 0.6 | 525 | 2 | 0.4 | 0.6423 | 0.68 | (0.14, 3.43) | 0.68 | (0.13, 3.46) | 0.00 | (-0.01, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.6480 |
| Low, moderate or high | 2430 | 6 | 0.2 | 2495 | 9 | 0.4 | 0.4762 | 1.45 | (0.52, 4.08) | 1.45 | (0.52, 4.09) | 0.00 | ( 0.00, 0.00) | |
| Very high | 834 | 7 | 0.8 | 820 | 7 | 0.9 | 0.9428 | 1.04 | (0.38, 2.85) | 1.04 | (0.37, 2.88) | 0.00 | (-0.01, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7642 |
| No | 572 | 2 | 0.3 | 578 | 3 | 0.5 | 0.6870 | 1.39 | (0.28, 7.02) | 1.40 | (0.27, 7.10) | 0.00 | (-0.01, 0.01) | |
| Yes | 2703 | 12 | 0.4 | 2752 | 13 | 0.5 | 0.8880 | 1.06 | (0.48, 2.31) | 1.06 | (0.48, 2.32) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8422 |
| No | 344 | 3 | 0.9 | 349 | 4 | 1.1 | 0.7473 | 1.25 | (0.32, 4.93) | 1.26 | (0.31, 5.06) | 0.00 | (-0.01, 0.02) | |
| Yes | 2931 | 11 | 0.4 | 2981 | 12 | 0.4 | 0.8798 | 1.06 | (0.47, 2.41) | 1.07 | (0.47, 2.42) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Pyelonephritis or Urosepsis (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4262 |
| No | 275 | 1 | 0.4 | 307 | 0 | 0 | 0.4899 | 0.44 | (0.04, 4.88) | 0.44 | (0.04, 4.88) | 0.00 | (-0.02, 0.01) | |
| Yes | 3000 | 13 | 0.4 | 3023 | 16 | 0.5 | 0.5990 | 1.22 | (0.59, 2.52) | 1.22 | (0.58, 2.54) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 31 | 0.9 | 3330 | 43 | 1.3 | 0.1880 | 1.36 | (0.86, 2.15) | 1.36 | (0.86, 2.17) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.9141 |
| 1245.110 | 2001 | 24 | 1.2 | 2052 | 33 | 1.6 | 0.2692 | 1.34 | (0.80, 2.26) | 1.35 | (0.79, 2.29) | 0.00 | ( 0.00, 0.01) | |
| 1245.121 | 1274 | 7 | 0.5 | 1278 | 10 | 0.8 | 0.4694 | 1.42 | (0.54, 3.73) | 1.43 | (0.54, 3.76) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.5924 |
| Male | 2023 | 17 | 0.8 | 2068 | 21 | 1.0 | 0.5624 | 1.21 | (0.64, 2.28) | 1.21 | (0.64, 2.30) | 0.00 | ( 0.00, 0.01) | |
| Female | 1252 | 14 | 1.1 | 1262 | 22 | 1.7 | 0.1926 | 1.55 | (0.80, 3.02) | 1.56 | (0.79, 3.07) | 0.01 | ( 0.00, 0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.4728 |
| <65 | 766 | 5 | 0.7 | 705 | 4 | 0.6 | 0.8210 | 0.86 | (0.23, 3.19) | 0.86 | (0.23, 3.22) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 26 | 1.0 | 2625 | 39 | 1.5 | 0.1479 | 1.44 | (0.88, 2.35) | 1.44 | (0.88, 2.38) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.6018 |
| North America | 434 | 9 | 2.1 | 432 | 7 | 1.6 | 0.6272 | 0.79 | (0.31, 2.04) | 0.79 | (0.30, 2.07) | 0.00 | (-0.02, 0.01) | |
| Latin America | 931 | 4 | 0.4 | 944 | 9 | 1.0 | 0.1667 | 2.24 | (0.69, 7.26) | 2.25 | (0.69, 7.36) | 0.01 | ( 0.00, 0.01) | |
| Europe | 1334 | 10 | 0.7 | 1361 | 18 | 1.3 | 0.1424 | 1.76 | (0.82, 3.81) | 1.77 | (0.82, 3.86) | 0.01 | ( 0.00, 0.01) | |
| Asia | 405 | 4 | 1.0 | 413 | 4 | 1.0 | 0.9477 | 0.96 | (0.26, 3.54) | 0.96 | (0.26, 3.58) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 4 | 2.3 | 180 | 5 | 2.8 | 0.8459 | 1.13 | (0.33, 3.85) | 1.13 | (0.32, 4.03) | 0.00 | (-0.03, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.4239 |
| Diabetic | 1739 | 15 | 0.9 | 1779 | 25 | 1.4 | 0.1332 | 1.62 | (0.86, 3.07) | 1.63 | (0.86, 3.11) | 0.01 | ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 16 | 1.0 | 1551 | 18 | 1.2 | 0.7555 | 1.11 | (0.57, 2.17) | 1.11 | (0.57, 2.19) | 0.00 | (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5055 |
| <30 | 1975 | 21 | 1.1 | 1930 | 25 | 1.3 | 0.5190 | 1.21 | (0.68, 2.15) | 1.21 | (0.68, 2.17) | 0.00 | ( 0.00, 0.01) | |
| >=30 | 1300 | 10 | 0.8 | 1400 | 18 | 1.3 | 0.1785 | 1.67 | (0.78, 3.55) | 1.68 | (0.78, 3.60) | 0.01 | ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6291 |
| <130 | 1684 | 17 | 1.0 | 1687 | 21 | 1.2 | 0.5423 | 1.22 | (0.65, 2.30) | 1.22 | (0.64, 2.32) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 1591 | 14 | 0.9 | 1643 | 22 | 1.3 | 0.2089 | 1.53 | (0.78, 2.98) | 1.54 | (0.78, 3.01) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3521 |
| <75 | 1653 | 22 | 1.3 | 1612 | 24 | 1.5 | 0.7256 | 1.11 | (0.62, 1.97) | 1.11 | (0.62, 1.99) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 6 | 0.6 | 1085 | 16 | 1.5 | 0.0542 | 2.36 | (0.96, 5.83) | 2.39 | (0.96, 5.95) | 0.01 | ( 0.00, 0.02) | |
| >=85 | 617 | 3 | 0.5 | 633 | 3 | 0.5 | 0.9752 | 0.97 | (0.20, 4.81) | 0.97 | (0.20, 4.85) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3516 |
| <30 | 250 | 1 | 0.4 | 263 | 6 | 2.3 | 0.0743 | 4.29 | (0.75,24.59) | 4.38 | (0.74,25.86) | 0.02 | ( 0.00, 0.04) | |
| 30 to <45 | 898 | 13 | 1.4 | 909 | 14 | 1.5 | 0.8875 | 1.06 | (0.50, 2.23) | 1.06 | (0.49, 2.26) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 17 | 0.8 | 2158 | 23 | 1.1 | 0.3741 | 1.33 | (0.71, 2.47) | 1.33 | (0.71, 2.50) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9407 |
| Normal (<30) | 1216 | 10 | 0.8 | 1243 | 13 | 1.0 | 0.5686 | 1.27 | (0.56, 2.88) | 1.27 | (0.56, 2.91) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 15 | 1.0 | 1546 | 23 | 1.5 | 0.1998 | 1.52 | (0.80, 2.90) | 1.53 | (0.79, 2.94) | 0.01 | ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 500 | 5 | 1.0 | 525 | 7 | 1.3 | 0.6086 | 1.34 | (0.43, 4.19) | 1.35 | (0.43, 4.27) | 0.00 | (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.6967 |
| Low, moderate or high | 2430 | 19 | 0.8 | 2495 | 26 | 1.0 | 0.3461 | 1.33 | (0.74, 2.39) | 1.33 | (0.73, 2.41) | 0.00 | ( 0.00, 0.01) | |
| Very high | 834 | 11 | 1.3 | 820 | 17 | 2.1 | 0.2141 | 1.60 | (0.76, 3.40) | 1.62 | (0.75, 3.49) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5983 |
| No | 572 | 9 | 1.6 | 578 | 10 | 1.7 | 0.8209 | 1.11 | (0.45, 2.70) | 1.11 | (0.45, 2.76) | 0.00 | (-0.01, 0.02) | |
| Yes | 2703 | 22 | 0.8 | 2752 | 33 | 1.2 | 0.1595 | 1.47 | (0.86, 2.51) | 1.47 | (0.86, 2.53) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3809 |
| No | 344 | 5 | 1.5 | 349 | 4 | 1.1 | 0.7321 | 0.80 | (0.23, 2.81) | 0.80 | (0.23, 2.83) | 0.00 | (-0.02, 0.01) | |
| Yes | 2931 | 26 | 0.9 | 2981 | 39 | 1.3 | 0.1262 | 1.47 | (0.90, 2.40) | 1.47 | (0.89, 2.43) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Bone fracture events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2130 |
| No | 275 | 1 | 0.4 | 307 | 6 | 2.0 | 0.1023 | 3.87 | (0.67,22.41) | 3.93 | (0.67,23.18) | 0.02 | ( 0.00, 0.03) | |
| Yes | 3000 | 30 | 1.0 | 3023 | 37 | 1.2 | 0.4152 | 1.22 | (0.76, 1.97) | 1.22 | (0.75, 1.98) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 7 | 0.2 | 3330 | 10 | 0.3 | 0.4852 | 1.41 | (0.54, 3.70) | 1.41 | (0.54, 3.71) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | |
| 1245.110 | 2001 | 3 | 0.1 | 2052 | 6 | 0.3 | | | | | | | | |
| 1245.121 | 1274 | 4 | 0.3 | 1278 | 4 | 0.3 | | | | | | | | |
| Sex | | | | | | | | | | | | | | 0.6614 |
| Male | 2023 | 5 | 0.2 | 2068 | 8 | 0.4 | 0.4276 | 1.56 | (0.51, 4.77) | 1.57 | (0.51, 4.80) | 0.00 | ( 0.00, 0.00) | |
| Female | 1252 | 2 | 0.2 | 1262 | 2 | 0.2 | 0.9914 | 1.01 | (0.20, 5.08) | 1.01 | (0.20, 5.05) | 0.00 | ( 0.00, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.8306 |
| <65 | 766 | 1 | 0.1 | 705 | 1 | 0.1 | 0.9392 | 1.09 | (0.11,10.47) | 1.09 | (0.11,10.52) | 0.00 | ( 0.00, 0.00) | |
| >=65 | 2509 | 6 | 0.2 | 2625 | 9 | 0.3 | 0.4924 | 1.43 | (0.51, 4.02) | 1.43 | (0.51, 4.03) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | |
| North America | 434 | 2 | 0.5 | 432 | 1 | 0.2 | | | | | | | | |
| Latin America | 931 | 1 | 0.1 | 944 | 2 | 0.2 | | | | | | | | |
| Europe | 1334 | 4 | 0.3 | 1361 | 4 | 0.3 | | | | | | | | |
| Asia | 405 | 0 | 0 | 413 | 3 | 0.7 | | | | | | | | |
| Other | 171 | 0 | 0 | 180 | 0 | 0 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5756 |
| Diabetic | 1739 | 4 | 0.2 | 1779 | 7 | 0.4 | 0.3815 | 1.72 | (0.50, 5.85) | 1.72 | (0.50, 5.89) | 0.00 | ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 3 | 0.2 | 1551 | 3 | 0.2 | 0.9906 | 0.99 | (0.22, 4.37) | 0.99 | (0.22, 4.37) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5977 |
| <30 | 1975 | 6 | 0.3 | 1930 | 7 | 0.4 | 0.7330 | 1.21 | (0.41, 3.59) | 1.21 | (0.41, 3.61) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1300 | 1 | 0.1 | 1400 | 3 | 0.2 | 0.4101 | 2.18 | (0.33,14.62) | 2.18 | (0.32,14.75) | 0.00 | ( 0.00, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3011 |
| <130 | 1684 | 4 | 0.2 | 1687 | 8 | 0.5 | 0.2488 | 2.00 | (0.60, 6.69) | 2.01 | (0.60, 6.70) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 1591 | 3 | 0.2 | 1643 | 2 | 0.1 | 0.6243 | 0.64 | (0.11, 3.85) | 0.64 | (0.11, 3.85) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2017 |
| <75 | 1653 | 4 | 0.2 | 1612 | 9 | 0.6 | 0.1504 | 2.32 | (0.71, 7.58) | 2.33 | (0.71, 7.60) | 0.00 | ( 0.00, 0.01) | |
| 75 to <85 | 1005 | 0 | 0 | 1085 | 1 | 0.1 | 0.6136 | 1.84 | (0.17,20.32) | 1.84 | (0.17,20.38) | 0.00 | ( 0.00, 0.00) | |
| >=85 | 617 | 3 | 0.5 | 633 | 0 | 0 | 0.1694 | 0.24 | (0.03, 2.17) | 0.24 | (0.03, 2.17) | 0.00 | (-0.01, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3397 |
| <30 | 250 | 2 | 0.8 | 263 | 1 | 0.4 | 0.5566 | 0.56 | (0.08, 3.99) | 0.56 | (0.07, 4.15) | 0.00 | (-0.02, 0.01) | |
| 30 to <45 | 898 | 1 | 0.1 | 909 | 0 | 0 | 0.5555 | 0.49 | (0.05, 5.41) | 0.49 | (0.04, 5.44) | 0.00 | ( 0.00, 0.00) | |
| >=45 | 2126 | 4 | 0.2 | 2158 | 9 | 0.4 | 0.1679 | 2.25 | (0.69, 7.32) | 2.25 | (0.69, 7.34) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | |
| Normal (<30) | 1216 | 2 | 0.2 | 1243 | 3 | 0.2 | | | | | | | | |
| Microalbuminuria (30 to <=300) | 1548 | 3 | 0.2 | 1546 | 6 | 0.4 | | | | | | | | |
| Macroalbuminuria (>300) | 500 | 2 | 0.4 | 525 | 1 | 0.2 | | | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7015 |
| Low, moderate or high | 2430 | 5 | 0.2 | 2495 | 8 | 0.3 | 0.4279 | 1.57 | (0.51, 4.80) | 1.57 | (0.51, 4.81) | 0.00 | ( 0.00, 0.00) | |
| Very high | 834 | 2 | 0.2 | 820 | 2 | 0.2 | 0.9936 | 1.01 | (0.14, 7.14) | 1.01 | (0.14, 7.17) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2629 |
| No | 572 | 0 | 0 | 578 | 3 | 0.5 | 0.1848 | 3.93 | (0.44,34.95) | 3.95 | (0.44,35.45) | 0.01 | ( 0.00, 0.01) | |
| Yes | 2703 | 7 | 0.3 | 2752 | 7 | 0.3 | 0.9780 | 0.99 | (0.35, 2.81) | 0.99 | (0.34, 2.81) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1479 |
| No | 344 | 2 | 0.6 | 349 | 0 | 0 | 0.2853 | 0.31 | (0.03, 2.97) | 0.31 | (0.03, 3.00) | -0.01 | (-0.02, 0.01) | |
| Yes | 2931 | 5 | 0.2 | 2981 | 10 | 0.3 | 0.2063 | 1.97 | (0.67, 5.78) | 1.98 | (0.67, 5.79) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Urinary tract malignancy events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.5140 |
| No | 275 | 0 | 0 | 307 | 2 | 0.7 | 0.3915 | 2.59 | (0.27,24.58) | 2.61 | (0.27,25.36) | 0.01 | (-0.01, 0.02) | |
| Yes | 3000 | 7 | 0.2 | 3023 | 8 | 0.3 | 0.8054 | 1.14 | (0.41, 3.13) | 1.14 | (0.41, 3.14) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 44 | 1.3 | 3330 | 56 | 1.7 | 0.2636 | 1.25 | (0.84, 1.85) | 1.25 | (0.84, 1.87) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.1009 |
| 1245.110 | 2001 | 26 | 1.3 | 2052 | 42 | 2.0 | 0.0640 | 1.58 | (0.97, 2.56) | 1.59 | (0.97, 2.60) | 0.01 | ( 0.00, 0.02) | |
| 1245.121 | 1274 | 18 | 1.4 | 1278 | 14 | 1.1 | 0.4713 | 0.78 | (0.39, 1.55) | 0.77 | (0.38, 1.56) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.5736 |
| Male | 2023 | 32 | 1.6 | 2068 | 38 | 1.8 | 0.5309 | 1.16 | (0.73, 1.85) | 1.16 | (0.72, 1.87) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 12 | 1.0 | 1262 | 18 | 1.4 | 0.2813 | 1.49 | (0.72, 3.08) | 1.49 | (0.72, 3.12) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.9743 |
| <65 | 766 | 8 | 1.0 | 705 | 9 | 1.3 | 0.6711 | 1.23 | (0.48, 3.17) | 1.23 | (0.47, 3.21) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 36 | 1.4 | 2625 | 47 | 1.8 | 0.3099 | 1.25 | (0.81, 1.92) | 1.25 | (0.81, 1.94) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.5530 |
| North America | 434 | 15 | 3.5 | 432 | 24 | 5.6 | 0.1371 | 1.61 | (0.85, 3.02) | 1.64 | (0.85, 3.17) | 0.02 | (-0.01, 0.05) | |
| Latin America | 931 | 9 | 1.0 | 944 | 14 | 1.5 | 0.3053 | 1.54 | (0.67, 3.54) | 1.55 | (0.67, 3.59) | 0.01 | ( 0.00, 0.02) | |
| Europe | 1334 | 14 | 1.0 | 1361 | 12 | 0.9 | 0.6506 | 0.84 | (0.39, 1.80) | 0.84 | (0.39, 1.81) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 3 | 0.7 | 413 | 1 | 0.2 | 0.4207 | 0.50 | (0.09, 2.81) | 0.50 | (0.09, 2.77) | 0.00 | (-0.02, 0.01) | |
| Other | 171 | 3 | 1.8 | 180 | 5 | 2.8 | 0.5767 | 1.46 | (0.39, 5.47) | 1.47 | (0.38, 5.73) | 0.01 | (-0.02, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0314 |
| Diabetic | 1739 | 32 | 1.8 | 1779 | 29 | 1.6 | 0.6293 | 0.88 | (0.54, 1.46) | 0.88 | (0.53, 1.47) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 1536 | 12 | 0.8 | 1551 | 27 | 1.7 | 0.0172 | 2.23 | (1.13, 4.38) | 2.25 | (1.13, 4.45) | 0.01 | ( 0.00, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1662 |
| <30 | 1975 | 20 | 1.0 | 1930 | 32 | 1.7 | 0.0778 | 1.64 | (0.94, 2.87) | 1.65 | (0.94, 2.91) | 0.01 | ( 0.00, 0.01) | |
| >=30 | 1300 | 24 | 1.8 | 1400 | 24 | 1.7 | 0.8303 | 0.94 | (0.54, 1.65) | 0.94 | (0.53, 1.66) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9023 |
| <130 | 1684 | 26 | 1.5 | 1687 | 32 | 1.9 | 0.4356 | 1.23 | (0.73, 2.05) | 1.23 | (0.73, 2.07) | 0.00 | (-0.01, 0.01) | |
| >=130 | 1591 | 18 | 1.1 | 1643 | 24 | 1.5 | 0.4050 | 1.29 | (0.71, 2.34) | 1.29 | (0.70, 2.37) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5427 |
| <75 | 1653 | 28 | 1.7 | 1612 | 33 | 2.0 | 0.4607 | 1.21 | (0.73, 1.99) | 1.21 | (0.73, 2.01) | 0.00 | (-0.01, 0.01) | |
| 75 to <85 | 1005 | 9 | 0.9 | 1085 | 17 | 1.6 | 0.1651 | 1.75 | (0.79, 3.91) | 1.76 | (0.78, 3.97) | 0.01 | ( 0.00, 0.02) | |
| >=85 | 617 | 7 | 1.1 | 633 | 6 | 0.9 | 0.7604 | 0.85 | (0.30, 2.41) | 0.85 | (0.29, 2.44) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.7703 |
| <30 | 250 | 7 | 2.8 | 263 | 10 | 3.8 | 0.4272 | 1.47 | (0.57, 3.79) | 1.49 | (0.55, 4.00) | 0.01 | (-0.02, 0.04) | |
| 30 to <45 | 898 | 12 | 1.3 | 909 | 12 | 1.3 | 0.9700 | 0.98 | (0.44, 2.18) | 0.98 | (0.44, 2.20) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 25 | 1.2 | 2158 | 34 | 1.6 | 0.2632 | 1.34 | (0.80, 2.24) | 1.35 | (0.80, 2.26) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1775 |
| Normal (<30) | 1216 | 14 | 1.2 | 1243 | 14 | 1.1 | 0.9449 | 0.97 | (0.47, 2.03) | 0.97 | (0.46, 2.05) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 21 | 1.4 | 1546 | 36 | 2.3 | 0.0447 | 1.72 | (1.01, 2.93) | 1.73 | (1.01, 2.99) | 0.01 | ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 500 | 9 | 1.8 | 525 | 6 | 1.1 | 0.3854 | 0.64 | (0.23, 1.77) | 0.63 | (0.22, 1.79) | -0.01 | (-0.02, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4682 |
| Low, moderate or high | 2430 | 30 | 1.2 | 2495 | 35 | 1.4 | 0.6098 | 1.13 | (0.70, 1.84) | 1.14 | (0.70, 1.86) | 0.00 | ( 0.00, 0.01) | |
| Very high | 834 | 14 | 1.7 | 820 | 21 | 2.6 | 0.2014 | 1.54 | (0.79, 3.01) | 1.56 | (0.79, 3.08) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3760 |
| No | 572 | 10 | 1.7 | 578 | 17 | 2.9 | 0.1794 | 1.69 | (0.78, 3.65) | 1.71 | (0.78, 3.77) | 0.01 | (-0.01, 0.03) | |
| Yes | 2703 | 34 | 1.3 | 2752 | 39 | 1.4 | 0.6141 | 1.12 | (0.71, 1.78) | 1.13 | (0.71, 1.79) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6821 |
| No | 344 | 5 | 1.5 | 349 | 8 | 2.3 | 0.4245 | 1.53 | (0.53, 4.39) | 1.54 | (0.53, 4.53) | 0.01 | (-0.01, 0.03) | |
| Yes | 2931 | 39 | 1.3 | 2981 | 48 | 1.6 | 0.3770 | 1.21 | (0.79, 1.84) | 1.21 | (0.79, 1.85) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Volume depletion events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4652 |
| No | 275 | 3 | 1.1 | 307 | 7 | 2.3 | 0.2925 | 1.94 | (0.55, 6.80) | 1.96 | (0.55, 7.04) | 0.01 | (-0.01, 0.03) | |
| Yes | 3000 | 41 | 1.4 | 3023 | 49 | 1.6 | 0.4193 | 1.18 | (0.78, 1.79) | 1.19 | (0.78, 1.80) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 37 | 1.1 | 3330 | 50 | 1.5 | 0.1871 | 1.33 | (0.87, 2.03) | 1.33 | (0.87, 2.04) | 0.00 | ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | | 0.0372 |
| 1245.110 | 2001 | 20 | 1.0 | 2052 | 38 | 1.9 | 0.0224 | 1.85 | (1.08, 3.17) | 1.87 | (1.08, 3.22) | 0.01 | ( 0.00, 0.02) | |
| 1245.121 | 1274 | 17 | 1.3 | 1278 | 12 | 0.9 | 0.3461 | 0.70 | (0.34, 1.47) | 0.70 | (0.33, 1.47) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.7335 |
| Male | 2023 | 27 | 1.3 | 2068 | 35 | 1.7 | 0.3509 | 1.27 | (0.77, 2.09) | 1.27 | (0.77, 2.11) | 0.00 | ( 0.00, 0.01) | |
| Female | 1252 | 10 | 0.8 | 1262 | 15 | 1.2 | 0.3220 | 1.49 | (0.67, 3.31) | 1.50 | (0.67, 3.35) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.6650 |
| <65 | 766 | 8 | 1.0 | 705 | 8 | 1.1 | 0.8627 | 1.09 | (0.41, 2.90) | 1.09 | (0.41, 2.93) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 29 | 1.2 | 2625 | 42 | 1.6 | 0.1719 | 1.39 | (0.87, 2.22) | 1.39 | (0.86, 2.24) | 0.00 | ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | | 0.4591 |
| North America | 434 | 13 | 3.0 | 432 | 23 | 5.3 | 0.0866 | 1.78 | (0.91, 3.47) | 1.82 | (0.91, 3.64) | 0.02 | ( 0.00, 0.05) | |
| Latin America | 931 | 8 | 0.9 | 944 | 12 | 1.3 | 0.3812 | 1.48 | (0.61, 3.60) | 1.49 | (0.61, 3.66) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 11 | 0.8 | 1361 | 9 | 0.7 | 0.6187 | 0.80 | (0.33, 1.93) | 0.80 | (0.33, 1.94) | 0.00 | (-0.01, 0.00) | |
| Asia | 405 | 3 | 0.7 | 413 | 1 | 0.2 | 0.4207 | 0.50 | (0.09, 2.81) | 0.50 | (0.09, 2.77) | 0.00 | (-0.02, 0.01) | |
| Other | 171 | 2 | 1.2 | 180 | 5 | 2.8 | 0.3343 | 2.05 | (0.46, 9.04) | 2.08 | (0.46, 9.46) | 0.02 | (-0.02, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.1918 |
| Diabetic | 1739 | 25 | 1.4 | 1779 | 27 | 1.5 | 0.8464 | 1.05 | (0.61, 1.81) | 1.06 | (0.61, 1.83) | 0.00 | (-0.01, 0.01) | |
| Non-Diabetic | 1536 | 12 | 0.8 | 1551 | 23 | 1.5 | 0.0663 | 1.90 | (0.95, 3.80) | 1.91 | (0.95, 3.85) | 0.01 | ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9872 |
| <30 | 1975 | 20 | 1.0 | 1930 | 26 | 1.3 | 0.3285 | 1.34 | (0.75, 2.39) | 1.34 | (0.74, 2.41) | 0.00 | ( 0.00, 0.01) | |
| >=30 | 1300 | 17 | 1.3 | 1400 | 24 | 1.7 | 0.3661 | 1.33 | (0.72, 2.45) | 1.33 | (0.71, 2.49) | 0.00 | ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8455 |
| <130 | 1684 | 21 | 1.2 | 1687 | 29 | 1.7 | 0.2590 | 1.38 | (0.79, 2.41) | 1.38 | (0.79, 2.44) | 0.00 | ( 0.00, 0.01) | |
| >=130 | 1591 | 16 | 1.0 | 1643 | 21 | 1.3 | 0.4651 | 1.27 | (0.67, 2.39) | 1.27 | (0.67, 2.42) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7758 |
| <75 | 1653 | 23 | 1.4 | 1612 | 30 | 1.9 | 0.2914 | 1.34 | (0.78, 2.29) | 1.34 | (0.78, 2.32) | 0.00 | ( 0.00, 0.01) | |
| 75 to <85 | 1005 | 8 | 0.8 | 1085 | 14 | 1.3 | 0.2680 | 1.62 | (0.68, 3.84) | 1.63 | (0.68, 3.89) | 0.00 | ( 0.00, 0.01) | |
| >=85 | 617 | 6 | 1.0 | 633 | 6 | 0.9 | 0.9718 | 0.98 | (0.33, 2.89) | 0.98 | (0.33, 2.92) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.9990 |
| <30 | 250 | 6 | 2.4 | 263 | 8 | 3.0 | 0.5719 | 1.35 | (0.47, 3.85) | 1.36 | (0.46, 4.02) | 0.01 | (-0.02, 0.04) | |
| 30 to <45 | 898 | 9 | 1.0 | 909 | 12 | 1.3 | 0.5311 | 1.32 | (0.56, 3.11) | 1.32 | (0.55, 3.15) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 22 | 1.0 | 2158 | 30 | 1.4 | 0.2904 | 1.34 | (0.78, 2.33) | 1.35 | (0.77, 2.35) | 0.00 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5578 |
| Normal (<30) | 1216 | 11 | 0.9 | 1243 | 14 | 1.1 | 0.5897 | 1.24 | (0.57, 2.72) | 1.24 | (0.56, 2.75) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 19 | 1.2 | 1546 | 30 | 1.9 | 0.1127 | 1.58 | (0.89, 2.80) | 1.59 | (0.89, 2.84) | 0.01 | ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 500 | 7 | 1.4 | 525 | 6 | 1.1 | 0.7135 | 0.82 | (0.28, 2.40) | 0.82 | (0.27, 2.43) | 0.00 | (-0.02, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3593 |
| Low, moderate or high | 2430 | 26 | 1.1 | 2495 | 31 | 1.2 | 0.5763 | 1.16 | (0.69, 1.95) | 1.16 | (0.69, 1.96) | 0.00 | ( 0.00, 0.01) | |
| Very high | 834 | 11 | 1.3 | 820 | 19 | 2.3 | 0.1237 | 1.77 | (0.85, 3.68) | 1.79 | (0.84, 3.77) | 0.01 | ( 0.00, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.6222 |
| No | 572 | 8 | 1.4 | 578 | 13 | 2.2 | 0.2818 | 1.61 | (0.67, 3.85) | 1.62 | (0.67, 3.95) | 0.01 | (-0.01, 0.02) | |
| Yes | 2703 | 29 | 1.1 | 2752 | 37 | 1.3 | 0.3634 | 1.25 | (0.77, 2.03) | 1.25 | (0.77, 2.05) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.7697 |
| No | 344 | 5 | 1.5 | 349 | 8 | 2.3 | 0.4245 | 1.53 | (0.53, 4.39) | 1.54 | (0.53, 4.53) | 0.01 | (-0.01, 0.03) | |
| Yes | 2931 | 32 | 1.1 | 2981 | 42 | 1.4 | 0.2750 | 1.29 | (0.82, 2.04) | 1.29 | (0.81, 2.06) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hypotension events (BIcMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.6992 |
| No | 275 | 3 | 1.1 | 307 | 6 | 2.0 | 0.4249 | 1.68 (0.46, 6.08) | 1.69 (0.46, 6.27) | 0.01 (-0.01, 0.03) | |
| Yes | 3000 | 34 | 1.1 | 3023 | 44 | 1.5 | 0.2704 | 1.28 (0.82, 2.00) | 1.29 (0.82, 2.02) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 142 | 4.3 | 3330 | 110 | 3.3 | 0.0279 | 0.76 | (0.60, 0.97) | 0.75 | (0.58, 0.97) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.7422 |
| 1245.110 | 2001 | 95 | 4.7 | 2052 | 72 | 3.5 | 0.0473 | 0.74 | (0.55,<1.00) | 0.73 | (0.53, 1.00) | -0.01 | (-0.02, 0.00) | |
| 1245.121 | 1274 | 47 | 3.7 | 1278 | 38 | 3.0 | 0.3138 | 0.81 | (0.53, 1.23) | 0.80 | (0.52, 1.24) | -0.01 | (-0.02, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.9550 |
| Male | 2023 | 88 | 4.3 | 2068 | 68 | 3.3 | 0.0761 | 0.76 | (0.55, 1.03) | 0.75 | (0.54, 1.03) | -0.01 | (-0.02, 0.00) | |
| Female | 1252 | 54 | 4.3 | 1262 | 42 | 3.3 | 0.1871 | 0.77 | (0.52, 1.14) | 0.76 | (0.50, 1.14) | -0.01 | (-0.03, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.2120 |
| <65 | 766 | 30 | 3.9 | 705 | 28 | 4.0 | 0.9660 | 1.01 | (0.61, 1.67) | 1.01 | (0.60, 1.71) | 0.00 | (-0.02, 0.02) | |
| >=65 | 2509 | 112 | 4.5 | 2625 | 82 | 3.1 | 0.0120 | 0.70 | (0.53, 0.93) | 0.69 | (0.52, 0.92) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | 0.7051 |
| North America | 434 | 33 | 7.6 | 432 | 28 | 6.5 | 0.5189 | 0.85 | (0.52, 1.39) | 0.84 | (0.50, 1.42) | -0.01 | (-0.05, 0.02) | |
| Latin America | 931 | 43 | 4.6 | 944 | 40 | 4.2 | 0.7106 | 0.92 | (0.61, 1.41) | 0.92 | (0.59, 1.43) | 0.00 | (-0.02, 0.02) | |
| Europe | 1334 | 48 | 3.6 | 1361 | 30 | 2.2 | 0.0314 | 0.61 | (0.39, 0.96) | 0.60 | (0.38, 0.96) | -0.01 | (-0.03, 0.00) | |
| Asia | 405 | 10 | 2.5 | 413 | 7 | 1.7 | 0.4014 | 0.67 | (0.26, 1.73) | 0.66 | (0.25, 1.75) | -0.01 | (-0.03, 0.01) | |
| Other | 171 | 8 | 4.7 | 180 | 5 | 2.8 | 0.3387 | 0.60 | (0.21, 1.72) | 0.59 | (0.20, 1.76) | -0.02 | (-0.06, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0692 |
| Diabetic | 1739 | 82 | 4.7 | 1779 | 76 | 4.3 | 0.5169 | 0.90 | (0.67, 1.23) | 0.90 | (0.65, 1.24) | 0.00 | (-0.02, 0.01) | |
| Non-Diabetic | 1536 | 60 | 3.9 | 1551 | 34 | 2.2 | 0.0056 | 0.56 | (0.37, 0.85) | 0.55 | (0.36, 0.84) | -0.02 | (-0.03,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6204 |
| <30 | 1975 | 66 | 3.3 | 1930 | 52 | 2.7 | 0.2372 | 0.81 | (0.56, 1.15) | 0.80 | (0.55, 1.16) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1300 | 76 | 5.8 | 1400 | 58 | 4.1 | 0.0451 | 0.71 | (0.51, 0.99) | 0.70 | (0.49, 0.99) | -0.02 | (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.3696 |
| <130 | 1684 | 76 | 4.5 | 1687 | 52 | 3.1 | 0.0296 | 0.68 | (0.48, 0.96) | 0.67 | (0.47, 0.96) | -0.01 | (-0.03, 0.00) | |
| >=130 | 1591 | 66 | 4.1 | 1643 | 58 | 3.5 | 0.3709 | 0.85 | (0.60, 1.21) | 0.85 | (0.59, 1.22) | -0.01 | (-0.02, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.7444 |
| <75 | 1653 | 86 | 5.2 | 1612 | 60 | 3.7 | 0.0399 | 0.71 | (0.52, 0.99) | 0.70 | (0.50, 0.99) | -0.01 | (-0.03, 0.00) | |
| 75 to <85 | 1005 | 36 | 3.6 | 1085 | 31 | 2.9 | 0.3516 | 0.80 | (0.50, 1.28) | 0.79 | (0.49, 1.29) | -0.01 | (-0.02, 0.01) | |
| >=85 | 617 | 20 | 3.2 | 633 | 19 | 3.0 | 0.8180 | 0.93 | (0.50, 1.72) | 0.93 | (0.49, 1.76) | 0.00 | (-0.02, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5408 |
| <30 | 250 | 33 | 13.2 | 263 | 32 | 12.2 | 0.8429 | 0.95 | (0.60, 1.51) | 0.95 | (0.56, 1.60) | -0.01 | (-0.06, 0.05) | |
| 30 to <45 | 898 | 46 | 5.1 | 909 | 34 | 3.7 | 0.1501 | 0.73 | (0.47, 1.12) | 0.72 | (0.46, 1.13) | -0.01 | (-0.03, 0.01) | |
| >=45 | 2126 | 63 | 3.0 | 2158 | 44 | 2.0 | 0.0525 | 0.69 | (0.47, 1.01) | 0.68 | (0.46, 1.01) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.1065 |
| Normal (<30) | 1216 | 46 | 3.8 | 1243 | 32 | 2.6 | 0.0873 | 0.68 | (0.44, 1.06) | 0.67 | (0.42, 1.06) | -0.01 | (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 62 | 4.0 | 1546 | 38 | 2.5 | 0.0148 | 0.61 | (0.41, 0.91) | 0.60 | (0.40, 0.91) | -0.02 | (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 500 | 34 | 6.8 | 525 | 40 | 7.6 | 0.5842 | 1.13 | (0.73, 1.76) | 1.14 | (0.71, 1.84) | 0.01 | (-0.02, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2855 |
| Low, moderate or high | 2430 | 76 | 3.1 | 2495 | 53 | 2.1 | 0.0274 | 0.68 | (0.48, 0.96) | 0.67 | (0.47, 0.96) | -0.01 | (-0.02, 0.00) | |
| Very high | 834 | 66 | 7.9 | 820 | 57 | 7.0 | 0.4814 | 0.88 | (0.63, 1.24) | 0.88 | (0.61, 1.27) | -0.01 | (-0.03, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7048 |
| No | 572 | 34 | 5.9 | 578 | 24 | 4.2 | 0.1641 | 0.70 | (0.42, 1.16) | 0.68 | (0.40, 1.17) | -0.02 | (-0.04, 0.01) | |
| Yes | 2703 | 108 | 4.0 | 2752 | 86 | 3.1 | 0.0799 | 0.78 | (0.59, 1.03) | 0.77 | (0.58, 1.03) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3932 |
| No | 344 | 21 | 6.1 | 349 | 12 | 3.4 | 0.1094 | 0.58 | (0.29, 1.14) | 0.56 | (0.28, 1.15) | -0.03 | (-0.06, 0.01) | |
| Yes | 2931 | 121 | 4.1 | 2981 | 98 | 3.3 | 0.0850 | 0.80 | (0.61, 1.03) | 0.79 | (0.60, 1.03) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Acute renal failure (SMQ)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.9561 |
| No | 275 | 5 | 1.8 | 307 | 4 | 1.3 | 0.6323 | 0.74 | (0.22, 2.55) | 0.74 | (0.21, 2.59) | -0.01 | (-0.03, 0.02) | |
| Yes | 3000 | 137 | 4.6 | 3023 | 106 | 3.5 | 0.0356 | 0.77 | (0.60, 0.98) | 0.76 | (0.59, 0.98) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 10 | 0.3 | 3330 | 3 | 0.1 | 0.0488 | 0.30 | (0.08, 1.07) | 0.29 | (0.08, 1.07) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | |
| 1245.110 | 2001 | 5 | 0.2 | 2052 | 2 | 0.1 | | | | | | | | |
| 1245.121 | 1274 | 5 | 0.4 | 1278 | 1 | 0.1 | | | | | | | | |
| Sex | | | | | | | | | | | | | | |
| Male | 2023 | 6 | 0.3 | 2068 | 3 | 0.1 | | | | | | | | |
| Female | 1252 | 4 | 0.3 | 1262 | 0 | 0 | | | | | | | | |
| Age [years] | | | | | | | | | | | | | | 0.7584 |
| <65 | 766 | 3 | 0.4 | 705 | 0 | 0 | 0.2151 | 0.27 | (0.03, 2.46) | 0.27 | (0.03, 2.45) | 0.00 | (-0.01, 0.00) | |
| >=65 | 2509 | 7 | 0.3 | 2625 | 3 | 0.1 | 0.1812 | 0.41 | (0.11, 1.58) | 0.41 | (0.11, 1.58) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | |
| North America | 434 | 5 | 1.2 | 432 | 3 | 0.7 | | | | | | | | |
| Latin America | 931 | 1 | 0.1 | 944 | 0 | 0 | | | | | | | | |
| Europe | 1334 | 1 | 0.1 | 1361 | 0 | 0 | | | | | | | | |
| Asia | 405 | 2 | 0.5 | 413 | 0 | 0 | | | | | | | | |
| Other | 171 | 1 | 0.6 | 180 | 0 | 0 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | |
| Diabetic | 1739 | 5 | 0.3 | 1779 | 2 | 0.1 | | | | | | | | |
| Non-Diabetic | 1536 | 5 | 0.3 | 1551 | 1 | 0.1 | | | | | | | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6221 |
| <30 | 1975 | 7 | 0.4 | 1930 | 3 | 0.2 | 0.2211 | 0.44 | (0.11, 1.70) | 0.44 | (0.11, 1.70) | 0.00 | (-0.01, 0.00) | |
| >=30 | 1300 | 3 | 0.2 | 1400 | 0 | 0 | 0.1509 | 0.23 | (0.03, 2.06) | 0.23 | (0.03, 2.06) | 0.00 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | |
| <130 | 1684 | 5 | 0.3 | 1687 | 2 | 0.1 | | | | | | | | |
| >=130 | 1591 | 5 | 0.3 | 1643 | 1 | 0.1 | | | | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9688 |
| <75 | 1653 | 7 | 0.4 | 1612 | 3 | 0.2 | 0.2189 | 0.44 | (0.11, 1.69) | 0.44 | (0.11, 1.70) | 0.00 | (-0.01, 0.00) | |
| 75 to <85 | 1005 | 1 | 0.1 | 1085 | 0 | 0 | 0.5197 | 0.46 | (0.04, 5.12) | 0.46 | (0.04, 5.12) | 0.00 | ( 0.00, 0.00) | |
| >=85 | 617 | 2 | 0.3 | 633 | 0 | 0 | 0.2980 | 0.32 | (0.03, 3.06) | 0.32 | (0.03, 3.08) | 0.00 | (-0.01, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | |
| <30 | 250 | 1 | 0.4 | 263 | 2 | 0.8 | | | | | | | | |
| 30 to <45 | 898 | 5 | 0.6 | 909 | 0 | 0 | | | | | | | | |
| >=45 | 2126 | 4 | 0.2 | 2158 | 1 | <0.1 | | | | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | |
| Normal (<30) | 1216 | 7 | 0.6 | 1243 | 0 | 0 | | | | | | | | |
| Microalbuminuria (30 to <=300) | 1548 | 1 | 0.1 | 1546 | 1 | 0.1 | | | | | | | | |
| Macroalbuminuria (>300) | 500 | 2 | 0.4 | 525 | 2 | 0.4 | | | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | |
| Low, moderate or high | 2430 | 7 | 0.3 | 2495 | 0 | 0 | | | | | | | | |
| Very high | 834 | 3 | 0.4 | 820 | 3 | 0.4 | | | | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | |
| No | 572 | 3 | 0.5 | 578 | 2 | 0.3 | | | | | | | | |
| Yes | 2703 | 7 | 0.3 | 2752 | 1 | <0.1 | | | | | | | | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2442 |
| No | 344 | 1 | 0.3 | 349 | 1 | 0.3 | 0.9483 | 0.94 | (0.14, 6.35) | 0.94 | (0.13, 6.57) | 0.00 | (-0.01, 0.01) | |
| Yes | 2931 | 9 | 0.3 | 2981 | 2 | 0.1 | 0.0325 | 0.22 | (0.05, 1.01) | 0.22 | (0.05, 1.01) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Gout (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.4945 |
| No | 275 | 0 | 0 | 307 | 0 | 0 | 0.9161 | 0.86 | (0.05,13.65) | 0.86 | (0.05,13.88) | 0.00 | (-0.01, 0.01) | |
| Yes | 3000 | 10 | 0.3 | 3023 | 3 | 0.1 | 0.0506 | 0.30 | (0.08, 1.08) | 0.30 | (0.08, 1.08) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 8 | 0.2 | 3330 | 9 | 0.3 | 0.8319 | 1.11 | (0.43, 2.87) | 1.11 | (0.43, 2.88) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | |
| 1245.110 | 2001 | 4 | 0.2 | 2052 | 5 | 0.2 | | | | | | | | |
| 1245.121 | 1274 | 4 | 0.3 | 1278 | 4 | 0.3 | | | | | | | | |
| Sex | | | | | | | | | | | | | | 0.0891 |
| Male | 2023 | 8 | 0.4 | 2068 | 5 | 0.2 | 0.3832 | 0.61 | (0.20, 1.87) | 0.61 | (0.20, 1.87) | 0.00 | ( 0.00, 0.00) | |
| Female | 1252 | 0 | 0 | 1262 | 4 | 0.3 | 0.1027 | 5.01 | (0.58,43.12) | 5.03 | (0.58,43.27) | 0.00 | ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3137 |
| <65 | 766 | 4 | 0.5 | 705 | 2 | 0.3 | 0.5231 | 0.61 | (0.13, 2.84) | 0.61 | (0.13, 2.86) | 0.00 | (-0.01, 0.00) | |
| >=65 | 2509 | 4 | 0.2 | 2625 | 7 | 0.3 | 0.4054 | 1.67 | (0.49, 5.71) | 1.68 | (0.49, 5.73) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | |
| North America | 434 | 1 | 0.2 | 432 | 3 | 0.7 | | | | | | | | |
| Latin America | 931 | 4 | 0.4 | 944 | 2 | 0.2 | | | | | | | | |
| Europe | 1334 | 1 | 0.1 | 1361 | 2 | 0.1 | | | | | | | | |
| Asia | 405 | 1 | 0.2 | 413 | 1 | 0.2 | | | | | | | | |
| Other | 171 | 1 | 0.6 | 180 | 1 | 0.6 | | | | | | | | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5951 |
| Diabetic | 1739 | 8 | 0.5 | 1779 | 8 | 0.4 | 0.9683 | 0.98 | (0.37, 2.61) | 0.98 | (0.37, 2.62) | 0.00 | ( 0.00, 0.00) | |
| Non-Diabetic | 1536 | 0 | 0 | 1551 | 1 | 0.1 | 0.5697 | 1.98 | (0.18,21.87) | 1.98 | (0.18,21.90) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1280 |
| <30 | 1975 | 5 | 0.3 | 1930 | 2 | 0.1 | 0.2745 | 0.41 | (0.08, 2.13) | 0.41 | (0.08, 2.13) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1300 | 3 | 0.2 | 1400 | 7 | 0.5 | 0.2555 | 2.15 | (0.56, 8.32) | 2.16 | (0.56, 8.37) | 0.00 | ( 0.00, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | |
| <130 | 1684 | 4 | 0.2 | 1687 | 4 | 0.2 | | | | | | | | |
| >=130 | 1591 | 4 | 0.3 | 1643 | 5 | 0.3 | | | | | | | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** | |
| Baseline DBP [mmHg] | | | | | | | | | | | | |
| <75 | 1653 | 4 | 0.2 | 1612 | 2 | 0.1 | | | | | | |
| 75 to <85 | 1005 | 3 | 0.3 | 1085 | 6 | 0.6 | | | | | | |
| >=85 | 617 | 1 | 0.2 | 633 | 1 | 0.2 | | | | | | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | |
| <30 | 250 | 0 | 0 | 263 | 4 | 1.5 | | | | | | |
| 30 to <45 | 898 | 3 | 0.3 | 909 | 2 | 0.2 | | | | | | |
| >=45 | 2126 | 5 | 0.2 | 2158 | 3 | 0.1 | | | | | | |
| Baseline UACR [mg/g] | | | | | | | | | | | | |
| Normal (<30) | 1216 | 1 | 0.1 | 1243 | 3 | 0.2 | | | | | | |
| Microalbuminuria (30 to <=300) | 1548 | 4 | 0.3 | 1546 | 3 | 0.2 | | | | | | |
| Macroalbuminuria (>300) | 500 | 3 | 0.6 | 525 | 3 | 0.6 | | | | | | |
| Baseline KDIGO risk category | | | | | | | | | | | | |
| Low, moderate or high | 2430 | 5 | 0.2 | 2495 | 4 | 0.2 | | | | | | |
| Very high | 834 | 3 | 0.4 | 820 | 5 | 0.6 | | | | | | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.0915 |
| No | 572 | 0 | 0 | 578 | 4 | 0.7 | 0.1051 | 4.92 | (0.58,41.81) | 4.96 (0.58,42.48) | 0.01 ( 0.00, 0.02) | |
| Yes | 2703 | 8 | 0.3 | 2752 | 5 | 0.2 | 0.3913 | 0.62 | (0.20, 1.88) | 0.62 (0.20, 1.89) | 0.00 ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.6121 |
| No | 344 | 0 | 0 | 349 | 1 | 0.3 | 0.5851 | 1.91 | (0.18,20.47) | 1.92 (0.18,21.04) | 0.00 (-0.01, 0.01) | |
| Yes | 2931 | 8 | 0.3 | 2981 | 8 | 0.3 | 0.9784 | 0.99 | (0.37, 2.62) | 0.99 (0.37, 2.63) | 0.00 ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: ^Severe hypoglycaemic events (investigator-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8614 |
| No | 275 | 0 | 0 | 307 | 0 | 0 | 0.9161 | 0.86 | (0.05,13.65) | 0.86 | (0.05,13.88) | 0.00 | (-0.01, 0.01) | |
| Yes | 3000 | 8 | 0.3 | 3023 | 9 | 0.3 | 0.8180 | 1.12 | (0.43, 2.89) | 1.12 | (0.43, 2.90) | 0.00 | ( 0.00, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 18 | 0.5 | 3330 | 14 | 0.4 | 0.4457 | 0.76 | (0.38, 1.53) | 0.76 | (0.38, 1.53) | 0.00 | ( 0.00, 0.00) | |
| Study | | | | | | | | | | | | | | 0.1055 |
| 1245.110 | 2001 | 15 | 0.7 | 2052 | 8 | 0.4 | 0.1275 | 0.52 | (0.22, 1.22) | 0.52 | (0.22, 1.22) | 0.00 | (-0.01, 0.00) | |
| 1245.121 | 1274 | 3 | 0.2 | 1278 | 6 | 0.5 | 0.3188 | 1.99 | (0.50, 7.95) | 2.00 | (0.50, 8.01) | 0.00 | ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.9136 |
| Male | 2023 | 13 | 0.6 | 2068 | 10 | 0.5 | 0.4942 | 0.75 | (0.33, 1.71) | 0.75 | (0.33, 1.71) | 0.00 | (-0.01, 0.00) | |
| Female | 1252 | 5 | 0.4 | 1262 | 4 | 0.3 | 0.7461 | 0.82 | (0.24, 2.80) | 0.82 | (0.24, 2.83) | 0.00 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.8895 |
| <65 | 766 | 6 | 0.8 | 705 | 4 | 0.6 | 0.6006 | 0.72 | (0.20, 2.51) | 0.71 | (0.20, 2.54) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 12 | 0.5 | 2625 | 10 | 0.4 | 0.5951 | 0.80 | (0.34, 1.84) | 0.80 | (0.34, 1.85) | 0.00 | ( 0.00, 0.00) | |
| Region | | | | | | | | | | | | | | 0.5192 |
| North America | 434 | 4 | 0.9 | 432 | 2 | 0.5 | 0.4511 | 0.56 | (0.12, 2.60) | 0.56 | (0.12, 2.62) | 0.00 | (-0.02, 0.01) | |
| Latin America | 931 | 7 | 0.8 | 944 | 6 | 0.6 | 0.7678 | 0.85 | (0.28, 2.54) | 0.85 | (0.28, 2.54) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 4 | 0.3 | 1361 | 0 | 0 | 0.0985 | 0.20 | (0.02, 1.68) | 0.20 | (0.02, 1.68) | 0.00 | (-0.01, 0.00) | |
| Asia | 405 | 1 | 0.2 | 413 | 2 | 0.5 | 0.6229 | 1.64 | (0.22,12.18) | 1.65 | (0.22,12.43) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 2 | 1.2 | 180 | 4 | 2.2 | 0.5050 | 1.68 | (0.36, 7.79) | 1.70 | (0.35, 8.10) | 0.01 | (-0.02, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6170 |
| Diabetic | 1739 | 13 | 0.7 | 1779 | 9 | 0.5 | 0.3591 | 0.67 | (0.29, 1.57) | 0.67 | (0.29, 1.58) | 0.00 | (-0.01, 0.00) | |
| Non-Diabetic | 1536 | 5 | 0.3 | 1551 | 5 | 0.3 | 0.9862 | 0.99 | (0.29, 3.41) | 0.99 | (0.29, 3.42) | 0.00 | ( 0.00, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1463 |
| <30 | 1975 | 6 | 0.3 | 1930 | 8 | 0.4 | 0.5702 | 1.36 | (0.47, 3.90) | 1.36 | (0.47, 3.92) | 0.00 | ( 0.00, 0.00) | |
| >=30 | 1300 | 12 | 0.9 | 1400 | 6 | 0.4 | 0.1185 | 0.46 | (0.17, 1.25) | 0.46 | (0.17, 1.24) | 0.00 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0483 |
| <130 | 1684 | 13 | 0.8 | 1687 | 5 | 0.3 | 0.0554 | 0.38 | (0.14, 1.06) | 0.38 | (0.14, 1.07) | 0.00 | (-0.01, 0.00) | |
| >=130 | 1591 | 5 | 0.3 | 1643 | 9 | 0.5 | 0.3307 | 1.68 | (0.59, 4.79) | 1.68 | (0.59, 4.81) | 0.00 | ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6305 |
| <75 | 1653 | 10 | 0.6 | 1612 | 8 | 0.5 | 0.6668 | 0.82 | (0.32, 2.06) | 0.82 | (0.32, 2.07) | 0.00 | (-0.01, 0.00) | |
| 75 to <85 | 1005 | 6 | 0.6 | 1085 | 3 | 0.3 | 0.2844 | 0.50 | (0.14, 1.83) | 0.50 | (0.14, 1.83) | 0.00 | (-0.01, 0.00) | |
| >=85 | 617 | 2 | 0.3 | 633 | 3 | 0.5 | 0.7055 | 1.37 | (0.27, 6.92) | 1.37 | (0.27, 6.97) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4386 |
| <30 | 250 | 4 | 1.6 | 263 | 2 | 0.8 | 0.4364 | 0.54 | (0.11, 2.65) | 0.53 | (0.11, 2.60) | -0.01 | (-0.03, 0.01) | |
| 30 to <45 | 898 | 8 | 0.9 | 909 | 4 | 0.4 | 0.2523 | 0.52 | (0.17, 1.63) | 0.52 | (0.16, 1.63) | 0.00 | (-0.01, 0.00) | |
| >=45 | 2126 | 6 | 0.3 | 2158 | 8 | 0.4 | 0.6085 | 1.31 | (0.46, 3.75) | 1.32 | (0.46, 3.78) | 0.00 | ( 0.00, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6426 |
| Normal (<30) | 1216 | 7 | 0.6 | 1243 | 4 | 0.3 | 0.3423 | 0.56 | (0.16, 1.90) | 0.56 | (0.16, 1.90) | 0.00 | (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 5 | 0.3 | 1546 | 6 | 0.4 | 0.7519 | 1.21 | (0.37, 3.94) | 1.21 | (0.37, 3.97) | 0.00 | ( 0.00, 0.00) | |
| Macroalbuminuria (>300) | 500 | 6 | 1.2 | 525 | 4 | 0.8 | 0.5065 | 0.67 | (0.20, 2.22) | 0.66 | (0.20, 2.23) | 0.00 | (-0.02, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.7455 |
| Low, moderate or high | 2430 | 9 | 0.4 | 2495 | 8 | 0.3 | 0.7584 | 0.86 | (0.33, 2.22) | 0.86 | (0.33, 2.23) | 0.00 | ( 0.00, 0.00) | |
| Very high | 834 | 9 | 1.1 | 820 | 6 | 0.7 | 0.4674 | 0.68 | (0.24, 1.92) | 0.68 | (0.24, 1.93) | 0.00 | (-0.01, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9138 |
| No | 572 | 3 | 0.5 | 578 | 2 | 0.3 | 0.6780 | 0.71 | (0.14, 3.59) | 0.71 | (0.14, 3.61) | 0.00 | (-0.01, 0.01) | |
| Yes | 2703 | 15 | 0.6 | 2752 | 12 | 0.4 | 0.5272 | 0.78 | (0.37, 1.67) | 0.78 | (0.37, 1.67) | 0.00 | ( 0.00, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1181 |
| No | 344 | 1 | 0.3 | 349 | 4 | 1.1 | 0.2496 | 2.79 | (0.45,17.17) | 2.82 | (0.44,17.99) | 0.01 | (-0.01, 0.02) | |
| Yes | 2931 | 17 | 0.6 | 2981 | 10 | 0.3 | 0.1578 | 0.58 | (0.26, 1.25) | 0.57 | (0.26, 1.25) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

Table R.5.2.3: 3 Proportion of patients with severe adverse events of special interest and severe other specific AEs by user-defined category occurring up to the end of the study, overall and by subgroup - TS
User-defined AE category: Hyperkalaemia (user-defined)

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.2476 |
| No | 275 | 0 | 0 | 307 | 2 | 0.7 | 0.3760 | 2.64 (0.28,24.69) | 2.66 (0.28,25.42) | 0.01 (-0.01, 0.02) | |
| Yes | 3000 | 18 | 0.6 | 3023 | 12 | 0.4 | 0.2603 | 0.66 (0.32, 1.37) | 0.66 (0.32, 1.37) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
^Severe hypoglycaemic events were defined as events requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. Intensity of the event (mild/moderate/severe) was not considered in the definition.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study. ^ Not analysed because of zero events within at least one study, either overall or within subgroup.

**R.5.2.4**

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 1446 | 44.2 | 3330 | 1280 | 38.4 | <0.0001 | 0.87 | ( 0.82, 0.92) | 0.79 | (0.72, 0.87) | -0.06 | (-0.08,-0.03) | |
| Study | | | | | | | | | | | | | | 0.1998 |
| 1245.110 | 2001 | 873 | 43.6 | 2052 | 803 | 39.1 | 0.0037 | 0.90 | ( 0.83, 0.97) | 0.83 | (0.73, 0.94) | -0.04 | (-0.08,-0.01) | |
| 1245.121 | 1274 | 573 | 45.0 | 1278 | 477 | 37.3 | <0.0001 | 0.83 | ( 0.76, 0.91) | 0.73 | (0.62, 0.85) | -0.08 | (-0.11,-0.04) | |
| Sex | | | | | | | | | | | | | | 0.4076 |
| Male | 2023 | 921 | 45.5 | 2068 | 804 | 38.9 | <0.0001 | 0.85 | ( 0.79, 0.92) | 0.76 | (0.67, 0.86) | -0.07 | (-0.10,-0.04) | |
| Female | 1252 | 525 | 41.9 | 1262 | 476 | 37.7 | 0.0294 | 0.90 | ( 0.82, 0.99) | 0.84 | (0.71, 0.98) | -0.04 | (-0.08, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.7656 |
| <65 | 766 | 327 | 42.7 | 705 | 266 | 37.7 | 0.0555 | 0.89 | ( 0.78,>1.00) | 0.82 | (0.66, 1.01) | -0.05 | (-0.10, 0.00) | |
| >=65 | 2509 | 1119 | 44.6 | 2625 | 1014 | 38.6 | <0.0001 | 0.87 | ( 0.81, 0.92) | 0.78 | (0.70, 0.87) | -0.06 | (-0.09,-0.03) | |
| Region | | | | | | | | | | | | | | 0.6800 |
| North America | 434 | 232 | 53.5 | 432 | 218 | 50.5 | 0.3772 | 0.94 | ( 0.83, 1.07) | 0.89 | (0.68, 1.16) | -0.03 | (-0.10, 0.04) | |
| Latin America | 931 | 377 | 40.5 | 944 | 326 | 34.5 | 0.0080 | 0.85 | ( 0.76, 0.96) | 0.78 | (0.64, 0.94) | -0.06 | (-0.10,-0.02) | |
| Europe | 1334 | 582 | 43.6 | 1361 | 516 | 37.9 | 0.0026 | 0.87 | ( 0.79, 0.95) | 0.79 | (0.68, 0.92) | -0.06 | (-0.09,-0.02) | |
| Asia | 405 | 187 | 46.2 | 413 | 164 | 39.7 | 0.0672 | 0.86 | ( 0.73, 1.01) | 0.77 | (0.59, 1.02) | -0.06 | (-0.13, 0.00) | |
| Other | 171 | 68 | 39.8 | 180 | 56 | 31.1 | 0.0740 | 0.77 | ( 0.58, 1.03) | 0.67 | (0.43, 1.04) | -0.09 | (-0.19, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5660 |
| Diabetic | 1739 | 796 | 45.8 | 1779 | 698 | 39.2 | <0.0001 | 0.86 | ( 0.79, 0.93) | 0.76 | (0.67, 0.87) | -0.07 | (-0.10,-0.03) | |
| Non-Diabetic | 1536 | 650 | 42.3 | 1551 | 582 | 37.5 | 0.0066 | 0.89 | ( 0.81, 0.97) | 0.82 | (0.71, 0.95) | -0.05 | (-0.08,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3986 |
| <30 | 1975 | 882 | 44.7 | 1930 | 735 | 38.1 | <0.0001 | 0.85 | ( 0.79, 0.92) | 0.76 | (0.67, 0.86) | -0.07 | (-0.10,-0.04) | |
| >=30 | 1300 | 564 | 43.4 | 1400 | 545 | 38.9 | 0.0175 | 0.90 | ( 0.82, 0.98) | 0.83 | (0.71, 0.97) | -0.05 | (-0.08,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9283 |
| <130 | 1684 | 783 | 46.5 | 1687 | 682 | 40.4 | 0.0004 | 0.87 | ( 0.80, 0.94) | 0.78 | (0.68, 0.89) | -0.06 | (-0.09,-0.03) | |
| >=130 | 1591 | 663 | 41.7 | 1643 | 598 | 36.4 | 0.0022 | 0.87 | ( 0.80, 0.95) | 0.80 | (0.70, 0.92) | -0.05 | (-0.09,-0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0143 |
| <75 | 1653 | 742 | 44.9 | 1612 | 684 | 42.4 | 0.1555 | 0.95 | ( 0.87, 1.02) | 0.90 | (0.79, 1.04) | -0.02 | (-0.06, 0.01) | |
| 75 to <85 | 1005 | 441 | 43.9 | 1085 | 372 | 34.3 | <0.0001 | 0.78 | ( 0.70, 0.87) | 0.67 | (0.56, 0.80) | -0.10 | (-0.14,-0.05) | |
| >=85 | 617 | 263 | 42.6 | 633 | 224 | 35.4 | 0.0087 | 0.83 | ( 0.72, 0.95) | 0.74 | (0.59, 0.93) | -0.07 | (-0.13,-0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0499 |
| <30 | 250 | 127 | 50.8 | 263 | 137 | 52.1 | 0.7355 | 1.03 | ( 0.87, 1.22) | 1.06 | (0.75, 1.50) | 0.01 | (-0.07, 0.10) | |
| 30 to <45 | 898 | 415 | 46.2 | 909 | 382 | 42.0 | 0.0715 | 0.91 | ( 0.82, 1.01) | 0.84 | (0.70, 1.02) | -0.04 | (-0.09, 0.00) | |
| >=45 | 2126 | 904 | 42.5 | 2158 | 761 | 35.3 | <0.0001 | 0.83 | ( 0.77, 0.89) | 0.74 | (0.65, 0.83) | -0.07 | (-0.10,-0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3354 |
| Normal (<30) | 1216 | 504 | 41.4 | 1243 | 450 | 36.2 | 0.0075 | 0.87 | ( 0.79, 0.96) | 0.80 | (0.68, 0.94) | -0.05 | (-0.09,-0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 685 | 44.3 | 1546 | 615 | 39.8 | 0.0120 | 0.90 | ( 0.83, 0.98) | 0.83 | (0.72, 0.96) | -0.04 | (-0.08,-0.01) | |
| Macroalbuminuria (>300) | 500 | 253 | 50.6 | 525 | 212 | 40.4 | 0.0010 | 0.80 | ( 0.70, 0.91) | 0.66 | (0.52, 0.85) | -0.10 | (-0.16,-0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1104 |
| Low, moderate or high | 2430 | 1030 | 42.4 | 2495 | 898 | 36.0 | <0.0001 | 0.85 | ( 0.79, 0.91) | 0.76 | (0.68, 0.86) | -0.06 | (-0.09,-0.04) | |
| Very high | 834 | 412 | 49.4 | 820 | 380 | 46.3 | 0.2150 | 0.94 | ( 0.85, 1.04) | 0.88 | (0.73, 1.07) | -0.03 | (-0.08, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1632 |
| No | 572 | 274 | 47.9 | 578 | 261 | 45.2 | 0.3581 | 0.94 | ( 0.83, 1.07) | 0.90 | (0.71, 1.13) | -0.03 | (-0.08, 0.03) | |
| Yes | 2703 | 1172 | 43.4 | 2752 | 1019 | 37.0 | <0.0001 | 0.85 | ( 0.80, 0.91) | 0.77 | (0.69, 0.86) | -0.06 | (-0.09,-0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5446 |
| No | 344 | 156 | 45.3 | 349 | 145 | 41.5 | 0.3046 | 0.91 | ( 0.77, 1.08) | 0.85 | (0.63, 1.15) | -0.04 | (-0.11, 0.04) | |
| Yes | 2931 | 1290 | 44.0 | 2981 | 1135 | 38.1 | <0.0001 | 0.87 | ( 0.81, 0.92) | 0.78 | (0.70, 0.87) | -0.06 | (-0.08,-0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.5768 |
| No | 275 | 103 | 37.5 | 307 | 106 | 34.5 | 0.4793 | 0.92 ( 0.74, 1.15) | 0.89 (0.63, 1.24) | -0.03 (-0.11, 0.05) | |
| Yes | 3000 | 1343 | 44.8 | 3023 | 1174 | 38.8 | <0.0001 | 0.87 ( 0.82, 0.92) | 0.78 (0.71, 0.87) | -0.06 (-0.08,-0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 3275 | 1327 | 40.5 | 3330 | 1315 | 39.5 | 0.3621 | 0.97 ( 0.92, 1.03) | 0.95 (0.86, 1.05) | -0.01 (-0.03, 0.01) | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 1104 | 33.7 | 3330 | 1003 | 30.1 | 0.0015 | 0.89 | ( 0.83, 0.96) | 0.85 | (0.76, 0.94) | -0.04 | (-0.06,-0.01) | |
| Study | | | | | | | | | | | | | | 0.4658 |
| 1245.110 | 2001 | 727 | 36.3 | 2052 | 678 | 33.0 | 0.0278 | 0.91 | ( 0.84, 0.99) | 0.86 | (0.76, 0.98) | -0.03 | (-0.06, 0.00) | |
| 1245.121 | 1274 | 377 | 29.6 | 1278 | 325 | 25.4 | 0.0186 | 0.86 | ( 0.76, 0.98) | 0.81 | (0.68, 0.97) | -0.04 | (-0.08,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.2223 |
| Male | 2023 | 670 | 33.1 | 2068 | 633 | 30.6 | 0.0817 | 0.92 | ( 0.84, 1.01) | 0.89 | (0.78, 1.01) | -0.03 | (-0.05, 0.00) | |
| Female | 1252 | 434 | 34.7 | 1262 | 370 | 29.3 | 0.0036 | 0.84 | ( 0.75, 0.95) | 0.78 | (0.66, 0.92) | -0.05 | (-0.09,-0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.1802 |
| <65 | 766 | 284 | 37.1 | 705 | 255 | 36.2 | 0.6677 | 0.97 | ( 0.85, 1.11) | 0.95 | (0.77, 1.18) | -0.01 | (-0.06, 0.04) | |
| >=65 | 2509 | 820 | 32.7 | 2625 | 748 | 28.5 | 0.0012 | 0.87 | ( 0.80, 0.95) | 0.82 | (0.73, 0.92) | -0.04 | (-0.07,-0.02) | |
| Region | | | | | | | | | | | | | | 0.3549 |
| North America | 434 | 153 | 35.3 | 432 | 160 | 37.0 | 0.5895 | 1.05 | ( 0.88, 1.25) | 1.08 | (0.82, 1.43) | 0.02 | (-0.05, 0.08) | |
| Latin America | 931 | 331 | 35.6 | 944 | 278 | 29.4 | 0.0058 | 0.83 | ( 0.73, 0.95) | 0.76 | (0.62, 0.92) | -0.06 | (-0.10,-0.02) | |
| Europe | 1334 | 387 | 29.0 | 1361 | 348 | 25.6 | 0.0425 | 0.88 | ( 0.78,<1.00) | 0.84 | (0.71, 0.99) | -0.03 | (-0.07, 0.00) | |
| Asia | 405 | 159 | 39.3 | 413 | 147 | 35.6 | 0.2853 | 0.91 | ( 0.76, 1.08) | 0.86 | (0.65, 1.14) | -0.04 | (-0.10, 0.03) | |
| Other | 171 | 74 | 43.3 | 180 | 70 | 38.9 | 0.3557 | 0.89 | ( 0.69, 1.14) | 0.82 | (0.53, 1.25) | -0.05 | (-0.15, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6554 |
| Diabetic | 1739 | 701 | 40.3 | 1779 | 648 | 36.4 | 0.0154 | 0.90 | ( 0.83, 0.98) | 0.84 | (0.74, 0.97) | -0.04 | (-0.07,-0.01) | |
| Non-Diabetic | 1536 | 403 | 26.2 | 1551 | 355 | 22.9 | 0.0298 | 0.87 | ( 0.77, 0.99) | 0.83 | (0.71, 0.98) | -0.03 | (-0.06, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9291 |
| <30 | 1975 | 652 | 33.0 | 1930 | 569 | 29.5 | 0.0136 | 0.89 | ( 0.81, 0.98) | 0.84 | (0.74, 0.97) | -0.04 | (-0.07,-0.01) | |
| >=30 | 1300 | 452 | 34.8 | 1400 | 434 | 31.0 | 0.0442 | 0.90 | ( 0.80,<1.00) | 0.85 | (0.72, 1.00) | -0.04 | (-0.07, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4715 |
| <130 | 1684 | 555 | 33.0 | 1687 | 485 | 28.7 | 0.0061 | 0.87 | ( 0.79, 0.96) | 0.81 | (0.70, 0.94) | -0.04 | (-0.07,-0.01) | |
| >=130 | 1591 | 549 | 34.5 | 1643 | 518 | 31.5 | 0.0748 | 0.91 | ( 0.83, 1.01) | 0.88 | (0.76, 1.01) | -0.03 | (-0.06, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9830 |
| <75 | 1653 | 578 | 35.0 | 1612 | 506 | 31.4 | 0.0233 | 0.89 | ( 0.81, 0.98) | 0.84 | (0.73, 0.98) | -0.04 | (-0.07,-0.01) | |
| 75 to <85 | 1005 | 314 | 31.2 | 1085 | 305 | 28.1 | 0.1204 | 0.90 | ( 0.79, 1.03) | 0.86 | (0.71, 1.04) | -0.03 | (-0.07, 0.01) | |
| >=85 | 617 | 212 | 34.4 | 633 | 192 | 30.3 | 0.1295 | 0.88 | ( 0.75, 1.04) | 0.83 | (0.66, 1.06) | -0.04 | (-0.09, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0352 |
| <30 | 250 | 103 | 41.2 | 263 | 119 | 45.2 | 0.2305 | 1.13 | ( 0.93, 1.38) | 1.24 | (0.87, 1.77) | 0.05 | (-0.03, 0.14) | |
| 30 to <45 | 898 | 340 | 37.9 | 909 | 286 | 31.5 | 0.0036 | 0.83 | ( 0.73, 0.94) | 0.75 | (0.62, 0.91) | -0.06 | (-0.11,-0.02) | |
| >=45 | 2126 | 661 | 31.1 | 2158 | 598 | 27.7 | 0.0130 | 0.89 | ( 0.81, 0.98) | 0.85 | (0.74, 0.97) | -0.03 | (-0.06,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5010 |
| Normal (<30) | 1216 | 365 | 30.0 | 1243 | 327 | 26.3 | 0.0387 | 0.88 | ( 0.77, 0.99) | 0.83 | (0.70, 0.99) | -0.04 | (-0.07, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 523 | 33.8 | 1546 | 458 | 29.6 | 0.0112 | 0.87 | ( 0.79, 0.97) | 0.82 | (0.71, 0.96) | -0.04 | (-0.08,-0.01) | |
| Macroalbuminuria (>300) | 500 | 214 | 42.8 | 525 | 216 | 41.1 | 0.6305 | 0.97 | ( 0.84, 1.11) | 0.94 | (0.73, 1.21) | -0.01 | (-0.07, 0.05) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2262 |
| Low, moderate or high | 2430 | 754 | 31.0 | 2495 | 676 | 27.1 | 0.0019 | 0.87 | ( 0.80, 0.95) | 0.82 | (0.73, 0.93) | -0.04 | (-0.07,-0.01) | |
| Very high | 834 | 349 | 41.8 | 820 | 325 | 39.6 | 0.4091 | 0.95 | ( 0.85, 1.07) | 0.92 | (0.76, 1.12) | -0.02 | (-0.07, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3000 |
| No | 572 | 209 | 36.5 | 578 | 174 | 30.1 | 0.0212 | 0.82 | ( 0.70, 0.97) | 0.75 | (0.59, 0.96) | -0.06 | (-0.12,-0.01) | |
| Yes | 2703 | 895 | 33.1 | 2752 | 829 | 30.1 | 0.0149 | 0.91 | ( 0.84, 0.98) | 0.87 | (0.77, 0.97) | -0.03 | (-0.06,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9329 |
| No | 344 | 108 | 31.4 | 349 | 99 | 28.4 | 0.3653 | 0.90 | ( 0.72, 1.13) | 0.86 | (0.62, 1.19) | -0.03 | (-0.10, 0.04) | |
| Yes | 2931 | 996 | 34.0 | 2981 | 904 | 30.3 | 0.0020 | 0.89 | ( 0.83, 0.96) | 0.84 | (0.75, 0.94) | -0.04 | (-0.06,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.5368 |
| No | 275 | 86 | 31.3 | 307 | 79 | 25.7 | 0.1484 | 0.83 ( 0.64, 1.07) | 0.77 (0.53, 1.10) | -0.05 (-0.13, 0.02) | |
| Yes | 3000 | 1018 | 33.9 | 3023 | 924 | 30.6 | 0.0045 | 0.90 ( 0.84, 0.97) | 0.85 (0.77, 0.95) | -0.03 (-0.06,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 810 | 24.7 | 3330 | 796 | 23.9 | 0.4086 | 0.96 ( 0.89, 1.05) | 0.95 (0.85, 1.07) | -0.01 (-0.03, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 673 | 20.5 | 3330 | 706 | 21.2 | 0.5353 | 1.03 | ( 0.94, 1.13) | 1.04 (0.92, 1.17) | 0.01 (-0.01, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 687 | 21.0 | 3330 | 687 | 20.6 | 0.6947 | 0.98 ( 0.89, 1.08) | 0.98 (0.87, 1.10) | 0.00 (-0.02, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 563 | 17.2 | 3330 | 635 | 19.1 | 0.0514 | 1.11 (<1.00, 1.23) | 1.13 (1.00, 1.29) | 0.02 ( 0.00, 0.04) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 615 | 18.8 | 3330 | 548 | 16.5 | 0.0108 | 0.87 | ( 0.79, 0.97) | 0.85 | (0.75, 0.96) | -0.02 | (-0.04,-0.01) | |
| Study | | | | | | | | | | | | | | 0.7060 |
| 1245.110 | 2001 | 452 | 22.6 | 2052 | 410 | 20.0 | 0.0425 | 0.88 | ( 0.79,<1.00) | 0.86 | (0.74, 0.99) | -0.03 | (-0.05, 0.00) | |
| 1245.121 | 1274 | 163 | 12.8 | 1278 | 138 | 10.8 | 0.1181 | 0.84 | ( 0.68, 1.04) | 0.83 | (0.65, 1.05) | -0.02 | (-0.04, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0232 |
| Male | 2023 | 344 | 17.0 | 2068 | 275 | 13.3 | 0.0008 | 0.78 | ( 0.68, 0.90) | 0.75 | (0.63, 0.89) | -0.04 | (-0.06,-0.02) | |
| Female | 1252 | 271 | 21.6 | 1262 | 273 | 21.6 | 0.9294 | 0.99 | ( 0.86, 1.15) | 0.99 | (0.82, 1.20) | 0.00 | (-0.03, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.3355 |
| <65 | 766 | 118 | 15.4 | 705 | 85 | 12.1 | 0.0533 | 0.78 | ( 0.60,>1.00) | 0.74 | (0.55, 1.00) | -0.03 | (-0.07, 0.00) | |
| >=65 | 2509 | 497 | 19.8 | 2625 | 463 | 17.6 | 0.0478 | 0.89 | ( 0.80,<1.00) | 0.87 | (0.75, 1.00) | -0.02 | (-0.04, 0.00) | |
| Region | | | | | | | | | | | | | | 0.4626 |
| North America | 434 | 135 | 31.1 | 432 | 120 | 27.8 | 0.2726 | 0.89 | ( 0.73, 1.09) | 0.85 | (0.63, 1.14) | -0.03 | (-0.09, 0.03) | |
| Latin America | 931 | 121 | 13.0 | 944 | 103 | 10.9 | 0.1927 | 0.85 | ( 0.67, 1.09) | 0.83 | (0.62, 1.10) | -0.02 | (-0.05, 0.01) | |
| Europe | 1334 | 200 | 15.0 | 1361 | 200 | 14.7 | 0.7961 | 0.98 | ( 0.82, 1.17) | 0.97 | (0.79, 1.20) | 0.00 | (-0.03, 0.02) | |
| Asia | 405 | 128 | 31.6 | 413 | 99 | 24.0 | 0.0100 | 0.75 | ( 0.60, 0.93) | 0.66 | (0.49, 0.91) | -0.08 | (-0.14,-0.02) | |
| Other | 171 | 31 | 18.1 | 180 | 26 | 14.4 | 0.3281 | 0.79 | ( 0.49, 1.27) | 0.75 | (0.42, 1.33) | -0.04 | (-0.12, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6945 |
| Diabetic | 1739 | 310 | 17.8 | 1779 | 284 | 16.0 | 0.1240 | 0.89 | ( 0.77, 1.03) | 0.87 | (0.73, 1.04) | -0.02 | (-0.04, 0.01) | |
| Non-Diabetic | 1536 | 305 | 19.9 | 1551 | 264 | 17.0 | 0.0386 | 0.86 | ( 0.74, 0.99) | 0.82 | (0.69, 0.99) | -0.03 | (-0.06, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7013 |
| <30 | 1975 | 360 | 18.2 | 1930 | 305 | 15.8 | 0.0323 | 0.86 | ( 0.75, 0.99) | 0.83 | (0.70, 0.98) | -0.03 | (-0.05, 0.00) | |
| >=30 | 1300 | 255 | 19.6 | 1400 | 243 | 17.4 | 0.1705 | 0.90 | ( 0.77, 1.05) | 0.87 | (0.72, 1.06) | -0.02 | (-0.05, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7053 |
| <130 | 1684 | 304 | 18.1 | 1687 | 263 | 15.6 | 0.0404 | 0.86 | ( 0.74, 0.99) | 0.83 | (0.69, 0.99) | -0.03 | (-0.05, 0.00) | |
| >=130 | 1591 | 311 | 19.5 | 1643 | 285 | 17.3 | 0.1163 | 0.89 | ( 0.77, 1.03) | 0.87 | (0.72, 1.04) | -0.02 | (-0.05, 0.01) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1938 |
| <75 | 1653 | 319 | 19.3 | 1612 | 299 | 18.5 | 0.5085 | 0.95 | ( 0.83, 1.10) | 0.94 | (0.79, 1.12) | -0.01 | (-0.04, 0.02) | |
| 75 to <85 | 1005 | 173 | 17.2 | 1085 | 155 | 14.3 | 0.0691 | 0.83 | ( 0.68, 1.01) | 0.80 | (0.63, 1.02) | -0.03 | (-0.06, 0.00) | |
| >=85 | 617 | 123 | 19.9 | 633 | 94 | 14.8 | 0.0185 | 0.75 | ( 0.59, 0.95) | 0.70 | (0.52, 0.94) | -0.05 | (-0.09,-0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.3414 |
| <30 | 250 | 53 | 21.2 | 263 | 57 | 21.7 | 0.7143 | 1.06 | ( 0.76, 1.48) | 1.08 | (0.71, 1.66) | 0.01 | (-0.06, 0.08) | |
| 30 to <45 | 898 | 191 | 21.3 | 909 | 156 | 17.2 | 0.0226 | 0.80 | ( 0.66, 0.97) | 0.76 | (0.60, 0.96) | -0.04 | (-0.08,-0.01) | |
| >=45 | 2126 | 371 | 17.5 | 2158 | 335 | 15.5 | 0.0676 | 0.88 | ( 0.77, 1.01) | 0.86 | (0.73, 1.01) | -0.02 | (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8957 |
| Normal (<30) | 1216 | 237 | 19.5 | 1243 | 219 | 17.6 | 0.2159 | 0.90 | ( 0.76, 1.06) | 0.88 | (0.72, 1.08) | -0.02 | (-0.05, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 281 | 18.2 | 1546 | 243 | 15.7 | 0.0589 | 0.86 | ( 0.74, 1.01) | 0.83 | (0.69, 1.01) | -0.03 | (-0.05, 0.00) | |
| Macroalbuminuria (>300) | 500 | 94 | 18.8 | 525 | 83 | 15.8 | 0.2262 | 0.85 | ( 0.65, 1.11) | 0.82 | (0.59, 1.13) | -0.03 | (-0.07, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5338 |
| Low, moderate or high | 2430 | 437 | 18.0 | 2495 | 387 | 15.5 | 0.0139 | 0.86 | ( 0.76, 0.97) | 0.83 | (0.71, 0.96) | -0.03 | (-0.05,-0.01) | |
| Very high | 834 | 176 | 21.1 | 820 | 158 | 19.3 | 0.3933 | 0.92 | ( 0.76, 1.11) | 0.90 | (0.71, 1.15) | -0.02 | (-0.06, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7219 |
| No | 572 | 140 | 24.5 | 578 | 119 | 20.6 | 0.1216 | 0.84 | ( 0.68, 1.05) | 0.80 | (0.61, 1.06) | -0.04 | (-0.09, 0.01) | |
| Yes | 2703 | 475 | 17.6 | 2752 | 429 | 15.6 | 0.0395 | 0.88 | ( 0.78, 0.99) | 0.86 | (0.74, 0.99) | -0.02 | (-0.04, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9674 |
| No | 344 | 68 | 19.8 | 349 | 60 | 17.2 | 0.4170 | 0.88 | ( 0.64, 1.20) | 0.85 | (0.58, 1.25) | -0.02 | (-0.08, 0.03) | |
| Yes | 2931 | 547 | 18.7 | 2981 | 488 | 16.4 | 0.0153 | 0.87 | ( 0.78, 0.97) | 0.85 | (0.74, 0.97) | -0.02 | (-0.04, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.4636 |
| No | 275 | 55 | 20.0 | 307 | 60 | 19.5 | 0.9078 | 0.98 ( 0.71, 1.36) | 0.98 (0.65, 1.47) | 0.00 (-0.07, 0.06) | |
| Yes | 3000 | 560 | 18.7 | 3023 | 488 | 16.1 | 0.0078 | 0.86 ( 0.77, 0.96) | 0.83 (0.73, 0.95) | -0.03 (-0.04,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 565 | 17.3 | 3330 | 517 | 15.5 | 0.0528 | 0.90 ( 0.81,>1.00) | 0.88 (0.77, 1.00) | -0.02 (-0.04, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 530 | 16.2 | 3330 | 547 | 16.4 | 0.8086 | 1.01 ( 0.91, 1.13) | 1.02 (0.89, 1.16) | 0.00 (-0.02, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 474 | 14.5 | 3330 | 514 | 15.4 | 0.2903 | 1.06 ( 0.95, 1.19) | 1.08 (0.94, 1.23) | 0.01 (-0.01, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 420 | 12.8 | 3330 | 366 | 11.0 | 0.0204 | 0.86 | ( 0.75, 0.98) | 0.84 | (0.72, 0.97) | -0.02 | (-0.03, 0.00) | |
| Study | | | | | | | | | | | | | | 0.9444 |
| 1245.110 | 2001 | 277 | 13.8 | 2052 | 244 | 11.9 | 0.0634 | 0.86 | ( 0.73, 1.01) | 0.84 | (0.70, 1.01) | -0.02 | (-0.04, 0.00) | |
| 1245.121 | 1274 | 143 | 11.2 | 1278 | 122 | 9.5 | 0.1647 | 0.85 | ( 0.68, 1.07) | 0.83 | (0.65, 1.08) | -0.02 | (-0.04, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.6842 |
| Male | 2023 | 256 | 12.7 | 2068 | 219 | 10.6 | 0.0391 | 0.84 | ( 0.71, 0.99) | 0.82 | (0.67, 0.99) | -0.02 | (-0.04, 0.00) | |
| Female | 1252 | 164 | 13.1 | 1262 | 147 | 11.6 | 0.2475 | 0.88 | ( 0.72, 1.09) | 0.87 | (0.68, 1.10) | -0.02 | (-0.04, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.1714 |
| <65 | 766 | 101 | 13.2 | 705 | 94 | 13.3 | 0.9593 | 1.01 | ( 0.78, 1.31) | 1.01 | (0.74, 1.36) | 0.00 | (-0.03, 0.04) | |
| >=65 | 2509 | 319 | 12.7 | 2625 | 272 | 10.4 | 0.0085 | 0.82 | ( 0.70, 0.95) | 0.79 | (0.67, 0.94) | -0.02 | (-0.04,-0.01) | |
| Region | | | | | | | | | | | | | | 0.5205 |
| North America | 434 | 89 | 20.5 | 432 | 67 | 15.5 | 0.0561 | 0.76 | ( 0.57, 1.01) | 0.71 | (0.50, 1.01) | -0.05 | (-0.10, 0.00) | |
| Latin America | 931 | 92 | 9.9 | 944 | 81 | 8.6 | 0.3518 | 0.87 | ( 0.66, 1.16) | 0.86 | (0.63, 1.18) | -0.01 | (-0.04, 0.01) | |
| Europe | 1334 | 144 | 10.8 | 1361 | 117 | 8.6 | 0.0525 | 0.80 | ( 0.63,>1.00) | 0.78 | (0.60, 1.00) | -0.02 | (-0.04, 0.00) | |
| Asia | 405 | 59 | 14.6 | 413 | 65 | 15.7 | 0.6599 | 1.08 | ( 0.78, 1.49) | 1.09 | (0.74, 1.60) | 0.01 | (-0.04, 0.06) | |
| Other | 171 | 36 | 21.1 | 180 | 36 | 20.0 | 0.7761 | 0.94 | ( 0.62, 1.42) | 0.93 | (0.55, 1.56) | -0.01 | (-0.10, 0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8915 |
| Diabetic | 1739 | 222 | 12.8 | 1779 | 193 | 10.8 | 0.0758 | 0.85 | ( 0.71, 1.02) | 0.83 | (0.68, 1.02) | -0.02 | (-0.04, 0.00) | |
| Non-Diabetic | 1536 | 198 | 12.9 | 1551 | 173 | 11.2 | 0.1352 | 0.86 | ( 0.71, 1.05) | 0.85 | (0.68, 1.05) | -0.02 | (-0.04, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1863 |
| <30 | 1975 | 267 | 13.5 | 1930 | 209 | 10.8 | 0.0090 | 0.80 | ( 0.67, 0.95) | 0.77 | (0.64, 0.94) | -0.03 | (-0.05,-0.01) | |
| >=30 | 1300 | 153 | 11.8 | 1400 | 157 | 11.2 | 0.6813 | 0.96 | ( 0.78, 1.18) | 0.95 | (0.75, 1.21) | -0.01 | (-0.03, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2086 |
| <130 | 1684 | 211 | 12.5 | 1687 | 197 | 11.7 | 0.4292 | 0.93 | ( 0.77, 1.11) | 0.92 | (0.75, 1.13) | -0.01 | (-0.03, 0.01) | |
| >=130 | 1591 | 209 | 13.1 | 1643 | 169 | 10.3 | 0.0124 | 0.78 | ( 0.65, 0.95) | 0.76 | (0.61, 0.94) | -0.03 | (-0.05,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0549 |
| <75 | 1653 | 208 | 12.6 | 1612 | 203 | 12.6 | 0.9822 | 1.00 | ( 0.83, 1.20) | 1.00 | (0.81, 1.23) | 0.00 | (-0.02, 0.02) | |
| 75 to <85 | 1005 | 123 | 12.2 | 1085 | 101 | 9.3 | 0.0314 | 0.76 | ( 0.59, 0.98) | 0.74 | (0.56, 0.97) | -0.03 | (-0.06, 0.00) | |
| >=85 | 617 | 89 | 14.4 | 633 | 62 | 9.8 | 0.0123 | 0.68 | ( 0.50, 0.92) | 0.65 | (0.46, 0.91) | -0.05 | (-0.08,-0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.8324 |
| <30 | 250 | 40 | 16.0 | 263 | 39 | 14.8 | 0.8463 | 0.96 | ( 0.64, 1.44) | 0.95 | (0.59, 1.55) | -0.01 | (-0.07, 0.06) | |
| 30 to <45 | 898 | 114 | 12.7 | 909 | 100 | 11.0 | 0.2575 | 0.86 | ( 0.67, 1.11) | 0.85 | (0.64, 1.13) | -0.02 | (-0.05, 0.01) | |
| >=45 | 2126 | 266 | 12.5 | 2158 | 227 | 10.5 | 0.0386 | 0.84 | ( 0.71, 0.99) | 0.82 | (0.68, 0.99) | -0.02 | (-0.04, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5389 |
| Normal (<30) | 1216 | 139 | 11.4 | 1243 | 128 | 10.3 | 0.3635 | 0.90 | ( 0.72, 1.13) | 0.89 | (0.69, 1.15) | -0.01 | (-0.04, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 204 | 13.2 | 1546 | 163 | 10.5 | 0.0220 | 0.80 | ( 0.66, 0.97) | 0.77 | (0.62, 0.96) | -0.03 | (-0.05, 0.00) | |
| Macroalbuminuria (>300) | 500 | 75 | 15.0 | 525 | 75 | 14.3 | 0.7737 | 0.96 | ( 0.71, 1.29) | 0.95 | (0.67, 1.34) | -0.01 | (-0.05, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9104 |
| Low, moderate or high | 2430 | 297 | 12.2 | 2495 | 265 | 10.6 | 0.0721 | 0.87 | ( 0.74, 1.01) | 0.85 | (0.71, 1.01) | -0.02 | (-0.03, 0.00) | |
| Very high | 834 | 121 | 14.5 | 820 | 101 | 12.3 | 0.2026 | 0.85 | ( 0.67, 1.09) | 0.83 | (0.63, 1.10) | -0.02 | (-0.05, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1323 |
| No | 572 | 80 | 14.0 | 578 | 84 | 14.5 | 0.7853 | 1.04 | ( 0.78, 1.38) | 1.05 | (0.75, 1.46) | 0.01 | (-0.03, 0.05) | |
| Yes | 2703 | 340 | 12.6 | 2752 | 282 | 10.2 | 0.0063 | 0.81 | ( 0.70, 0.94) | 0.79 | (0.67, 0.94) | -0.02 | (-0.04,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1120 |
| No | 344 | 57 | 16.6 | 349 | 37 | 10.6 | 0.0209 | 0.64 | ( 0.43, 0.94) | 0.59 | (0.38, 0.93) | -0.06 | (-0.11,-0.01) | |
| Yes | 2931 | 363 | 12.4 | 2981 | 329 | 11.0 | 0.1006 | 0.89 | ( 0.77, 1.02) | 0.88 | (0.75, 1.03) | -0.01 | (-0.03, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.5692 |
| No | 275 | 40 | 14.5 | 307 | 34 | 11.1 | 0.2076 | 0.76 ( 0.50, 1.17) | 0.73 (0.45, 1.19) | -0.03 (-0.09, 0.02) | |
| Yes | 3000 | 380 | 12.7 | 3023 | 332 | 11.0 | 0.0411 | 0.87 ( 0.75, 0.99) | 0.85 (0.73, 0.99) | -0.02 (-0.03, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 376 | 11.5 | 3330 | 301 | 9.0 | 0.0009 | 0.78 | ( 0.68, 0.91) | 0.76 | (0.65, 0.89) | -0.02 | (-0.04,-0.01) | |
| Study | | | | | | | | | | | | | | 0.7725 |
| 1245.110 | 2001 | 283 | 14.1 | 2052 | 225 | 11.0 | 0.0023 | 0.78 | ( 0.66, 0.91) | 0.75 | (0.62, 0.90) | -0.03 | (-0.05,-0.01) | |
| 1245.121 | 1274 | 93 | 7.3 | 1278 | 76 | 5.9 | 0.1694 | 0.81 | ( 0.61, 1.09) | 0.80 | (0.59, 1.10) | -0.01 | (-0.03, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.8356 |
| Male | 2023 | 233 | 11.5 | 2068 | 185 | 8.9 | 0.0060 | 0.78 | ( 0.65, 0.93) | 0.75 | (0.61, 0.92) | -0.03 | (-0.04,-0.01) | |
| Female | 1252 | 143 | 11.4 | 1262 | 116 | 9.2 | 0.0588 | 0.80 | ( 0.63, 1.01) | 0.78 | (0.60, 1.01) | -0.02 | (-0.05, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.7873 |
| <65 | 766 | 74 | 9.7 | 705 | 56 | 7.9 | 0.2301 | 0.82 | ( 0.59, 1.14) | 0.80 | (0.56, 1.15) | -0.02 | (-0.05, 0.01) | |
| >=65 | 2509 | 302 | 12.0 | 2625 | 245 | 9.3 | 0.0018 | 0.78 | ( 0.66, 0.91) | 0.75 | (0.63, 0.90) | -0.03 | (-0.04,-0.01) | |
| Region | | | | | | | | | | | | | | 0.0729 |
| North America | 434 | 70 | 16.1 | 432 | 36 | 8.3 | 0.0004 | 0.52 | ( 0.35, 0.75) | 0.47 | (0.31, 0.72) | -0.08 | (-0.12,-0.03) | |
| Latin America | 931 | 86 | 9.2 | 944 | 81 | 8.6 | 0.6891 | 0.94 | ( 0.71, 1.26) | 0.94 | (0.68, 1.29) | -0.01 | (-0.03, 0.02) | |
| Europe | 1334 | 147 | 11.0 | 1361 | 110 | 8.1 | 0.0087 | 0.73 | ( 0.58, 0.93) | 0.71 | (0.55, 0.92) | -0.03 | (-0.05,-0.01) | |
| Asia | 405 | 54 | 13.3 | 413 | 55 | 13.3 | 0.9222 | 0.98 | ( 0.69, 1.39) | 0.98 | (0.65, 1.47) | 0.00 | (-0.05, 0.04) | |
| Other | 171 | 19 | 11.1 | 180 | 19 | 10.6 | 0.8301 | 0.94 | ( 0.52, 1.70) | 0.93 | (0.47, 1.82) | -0.01 | (-0.07, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.1372 |
| Diabetic | 1739 | 207 | 11.9 | 1779 | 183 | 10.3 | 0.1149 | 0.86 | ( 0.71, 1.04) | 0.84 | (0.68, 1.04) | -0.02 | (-0.04, 0.00) | |
| Non-Diabetic | 1536 | 169 | 11.0 | 1551 | 118 | 7.6 | 0.0010 | 0.69 | ( 0.55, 0.86) | 0.66 | (0.52, 0.85) | -0.03 | (-0.05,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3136 |
| <30 | 1975 | 233 | 11.8 | 1930 | 192 | 9.9 | 0.0486 | 0.83 | ( 0.70,<1.00) | 0.82 | (0.67, 1.00) | -0.02 | (-0.04, 0.00) | |
| >=30 | 1300 | 143 | 11.0 | 1400 | 109 | 7.8 | 0.0055 | 0.72 | ( 0.57, 0.91) | 0.69 | (0.53, 0.90) | -0.03 | (-0.05,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.4123 |
| <130 | 1684 | 174 | 10.3 | 1687 | 147 | 8.7 | 0.0913 | 0.84 | ( 0.68, 1.03) | 0.82 | (0.65, 1.03) | -0.02 | (-0.04, 0.00) | |
| >=130 | 1591 | 202 | 12.7 | 1643 | 154 | 9.4 | 0.0029 | 0.74 | ( 0.61, 0.90) | 0.71 | (0.57, 0.89) | -0.03 | (-0.05,-0.01) | |

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System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6393 |
| <75 | 1653 | 207 | 12.5 | 1612 | 155 | 9.6 | 0.0059 | 0.76 | ( 0.63, 0.93) | 0.73 | (0.59, 0.91) | -0.03 | (-0.05,-0.01) | |
| 75 to <85 | 1005 | 108 | 10.7 | 1085 | 101 | 9.3 | 0.2823 | 0.87 | ( 0.67, 1.12) | 0.85 | (0.64, 1.14) | -0.01 | (-0.04, 0.01) | |
| >=85 | 617 | 61 | 9.9 | 633 | 45 | 7.1 | 0.0810 | 0.72 | ( 0.50, 1.04) | 0.70 | (0.47, 1.05) | -0.03 | (-0.06, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5372 |
| <30 | 250 | 48 | 19.2 | 263 | 40 | 15.2 | 0.3914 | 0.85 | ( 0.58, 1.23) | 0.82 | (0.51, 1.30) | -0.03 | (-0.09, 0.04) | |
| 30 to <45 | 898 | 116 | 12.9 | 909 | 82 | 9.0 | 0.0070 | 0.70 | ( 0.53, 0.91) | 0.66 | (0.49, 0.89) | -0.04 | (-0.07,-0.01) | |
| >=45 | 2126 | 212 | 10.0 | 2158 | 179 | 8.3 | 0.0465 | 0.83 | ( 0.68,<1.00) | 0.81 | (0.66, 1.00) | -0.02 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6241 |
| Normal (<30) | 1216 | 131 | 10.8 | 1243 | 98 | 7.9 | 0.0125 | 0.73 | ( 0.57, 0.94) | 0.70 | (0.53, 0.93) | -0.03 | (-0.05,-0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 175 | 11.3 | 1546 | 140 | 9.1 | 0.0324 | 0.80 | ( 0.65, 0.98) | 0.77 | (0.61, 0.98) | -0.02 | (-0.04, 0.00) | |
| Macroalbuminuria (>300) | 500 | 68 | 13.6 | 525 | 63 | 12.0 | 0.4754 | 0.89 | ( 0.65, 1.22) | 0.87 | (0.60, 1.26) | -0.01 | (-0.06, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.9506 |
| Low, moderate or high | 2430 | 246 | 10.1 | 2495 | 201 | 8.1 | 0.0090 | 0.79 | ( 0.66, 0.94) | 0.77 | (0.63, 0.94) | -0.02 | (-0.04,-0.01) | |
| Very high | 834 | 129 | 15.5 | 820 | 100 | 12.2 | 0.0650 | 0.80 | ( 0.63, 1.01) | 0.77 | (0.58, 1.02) | -0.03 | (-0.06, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2511 |
| No | 572 | 78 | 13.6 | 578 | 72 | 12.5 | 0.5654 | 0.92 | ( 0.68, 1.23) | 0.90 | (0.64, 1.28) | -0.01 | (-0.05, 0.03) | |
| Yes | 2703 | 298 | 11.0 | 2752 | 229 | 8.3 | 0.0005 | 0.75 | ( 0.64, 0.88) | 0.73 | (0.61, 0.87) | -0.03 | (-0.04,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3997 |
| No | 344 | 52 | 15.1 | 349 | 35 | 10.0 | 0.0472 | 0.67 | ( 0.44,<1.00) | 0.63 | (0.40, 1.00) | -0.05 | (-0.10, 0.00) | |
| Yes | 2931 | 324 | 11.1 | 2981 | 266 | 8.9 | 0.0049 | 0.80 | ( 0.69, 0.94) | 0.78 | (0.66, 0.93) | -0.02 | (-0.04,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.3935 |
| No | 275 | 25 | 9.1 | 307 | 27 | 8.8 | 0.9310 | 0.98 ( 0.58, 1.64) | 0.97 (0.55, 1.73) | 0.00 (-0.05, 0.04) | |
| Yes | 3000 | 351 | 11.7 | 3023 | 274 | 9.1 | 0.0006 | 0.77 ( 0.67, 0.90) | 0.75 (0.63, 0.88) | -0.03 (-0.04,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 319 | 9.7 | 3330 | 367 | 11.0 | 0.0913 | 1.13 ( 0.98, 1.30) | 1.15 (0.98, 1.34) | 0.01 ( 0.00, 0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 243 | 7.4 | 3330 | 246 | 7.4 | 0.9466 | 0.99 ( 0.84, 1.18) | 0.99 (0.83, 1.19) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

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System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 199 | 6.1 | 3330 | 208 | 6.2 | 0.8025 | 1.02 | ( 0.85, 1.24) | 1.03 (0.84, 1.25) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 151 | 4.6 | 3330 | 184 | 5.5 | 0.0948 | 1.20 ( 0.97, 1.47) | 1.21 (0.97, 1.51) | 0.01 ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 179 | 5.5 | 3330 | 151 | 4.5 | 0.0805 | 0.83 | ( 0.67, 1.02) | 0.82 (0.66, 1.02) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Reproductive system and breast disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 122 | 3.7 | 3330 | 133 | 4.0 | 0.5795 | 1.07 ( 0.84, 1.36) | 1.07 (0.84, 1.38) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Endocrine disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 106 | 3.2 | 3330 | 82 | 2.5 | 0.0580 | 0.76 | ( 0.57, 1.01) | 0.75 (0.56, 1.01) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Ear and labyrinth disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 84 | 2.6 | 3330 | 96 | 2.9 | 0.4416 | 1.12 ( 0.84, 1.49) | 1.12 (0.83, 1.51) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 1276 | 39.0 | 3330 | 1089 | 32.7 | <0.0001 | 0.84 | ( 0.79, 0.90) | 0.76 | (0.69, 0.84) | -0.06 | (-0.09,-0.04) | |
| Study | | | | | | | | | | | | | | 0.5713 |
| 1245.110 | 2001 | 749 | 37.4 | 2052 | 655 | 31.9 | 0.0002 | 0.85 | ( 0.78, 0.93) | 0.78 | (0.69, 0.89) | -0.06 | (-0.08,-0.03) | |
| 1245.121 | 1274 | 527 | 41.4 | 1278 | 434 | 34.0 | 0.0001 | 0.82 | ( 0.74, 0.91) | 0.73 | (0.62, 0.86) | -0.07 | (-0.11,-0.04) | |
| Sex | | | | | | | | | | | | | | 0.4360 |
| Male | 2023 | 826 | 40.8 | 2068 | 695 | 33.6 | <0.0001 | 0.82 | ( 0.76, 0.89) | 0.73 | (0.65, 0.83) | -0.07 | (-0.10,-0.04) | |
| Female | 1252 | 450 | 35.9 | 1262 | 394 | 31.2 | 0.0126 | 0.87 | ( 0.78, 0.97) | 0.81 | (0.69, 0.96) | -0.05 | (-0.08,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.4291 |
| <65 | 766 | 294 | 38.4 | 705 | 238 | 33.8 | 0.0703 | 0.88 | ( 0.77, 1.01) | 0.82 | (0.66, 1.02) | -0.05 | (-0.09, 0.00) | |
| >=65 | 2509 | 982 | 39.1 | 2625 | 851 | 32.4 | <0.0001 | 0.83 | ( 0.77, 0.89) | 0.75 | (0.67, 0.84) | -0.07 | (-0.09,-0.04) | |
| Region | | | | | | | | | | | | | | 0.6924 |
| North America | 434 | 209 | 48.2 | 432 | 188 | 43.5 | 0.1713 | 0.90 | ( 0.78, 1.04) | 0.83 | (0.63, 1.08) | -0.05 | (-0.11, 0.02) | |
| Latin America | 931 | 341 | 36.6 | 944 | 289 | 30.6 | 0.0058 | 0.84 | ( 0.74, 0.95) | 0.76 | (0.63, 0.93) | -0.06 | (-0.10,-0.02) | |
| Europe | 1334 | 493 | 37.0 | 1361 | 427 | 31.4 | 0.0024 | 0.85 | ( 0.77, 0.94) | 0.78 | (0.67, 0.92) | -0.06 | (-0.09,-0.02) | |
| Asia | 405 | 175 | 43.2 | 413 | 140 | 33.9 | 0.0076 | 0.79 | ( 0.66, 0.94) | 0.68 | (0.51, 0.90) | -0.09 | (-0.16,-0.02) | |
| Other | 171 | 58 | 33.9 | 180 | 45 | 25.0 | 0.0563 | 0.73 | ( 0.53, 1.01) | 0.64 | (0.40, 1.01) | -0.09 | (-0.19, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3484 |
| Diabetic | 1739 | 721 | 41.5 | 1779 | 602 | 33.8 | <0.0001 | 0.82 | ( 0.75, 0.89) | 0.72 | (0.63, 0.83) | -0.08 | (-0.11,-0.04) | |
| Non-Diabetic | 1536 | 555 | 36.1 | 1551 | 487 | 31.4 | 0.0055 | 0.87 | ( 0.79, 0.96) | 0.81 | (0.70, 0.94) | -0.05 | (-0.08,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3294 |
| <30 | 1975 | 779 | 39.4 | 1930 | 621 | 32.2 | <0.0001 | 0.82 | ( 0.75, 0.89) | 0.73 | (0.64, 0.83) | -0.07 | (-0.10,-0.04) | |
| >=30 | 1300 | 497 | 38.2 | 1400 | 468 | 33.4 | 0.0077 | 0.87 | ( 0.79, 0.96) | 0.81 | (0.69, 0.94) | -0.05 | (-0.09,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8321 |
| <130 | 1684 | 698 | 41.4 | 1687 | 591 | 35.0 | 0.0001 | 0.85 | ( 0.78, 0.92) | 0.76 | (0.66, 0.88) | -0.06 | (-0.10,-0.03) | |
| >=130 | 1591 | 578 | 36.3 | 1643 | 498 | 30.3 | 0.0003 | 0.83 | ( 0.76, 0.92) | 0.76 | (0.66, 0.88) | -0.06 | (-0.09,-0.03) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0302 |
| <75 | 1653 | 653 | 39.5 | 1612 | 582 | 36.1 | 0.0472 | 0.91 | ( 0.84, <1.00) | 0.87 | (0.75, 1.00) | -0.03 | (-0.07, 0.00) | |
| 75 to <85 | 1005 | 392 | 39.0 | 1085 | 324 | 29.9 | <0.0001 | 0.77 | ( 0.68, 0.86) | 0.67 | (0.55, 0.80) | -0.09 | (-0.13,-0.05) | |
| >=85 | 617 | 231 | 37.4 | 633 | 183 | 28.9 | 0.0013 | 0.77 | ( 0.66, 0.90) | 0.68 | (0.54, 0.86) | -0.09 | (-0.14,-0.03) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0484 |
| <30 | 250 | 116 | 46.4 | 263 | 124 | 47.1 | 0.8598 | 1.02 | ( 0.84, 1.22) | 1.03 | (0.73, 1.46) | 0.01 | (-0.08, 0.09) | |
| 30 to <45 | 898 | 370 | 41.2 | 909 | 328 | 36.1 | 0.0255 | 0.88 | ( 0.78, 0.98) | 0.81 | (0.67, 0.97) | -0.05 | (-0.10,-0.01) | |
| >=45 | 2126 | 790 | 37.2 | 2158 | 637 | 29.5 | <0.0001 | 0.80 | ( 0.73, 0.87) | 0.71 | (0.62, 0.81) | -0.08 | (-0.10,-0.05) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6266 |
| Normal (<30) | 1216 | 416 | 34.2 | 1243 | 366 | 29.4 | 0.0113 | 0.86 | ( 0.77, 0.97) | 0.80 | (0.68, 0.95) | -0.05 | (-0.08,-0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 622 | 40.2 | 1546 | 526 | 34.0 | 0.0004 | 0.85 | ( 0.77, 0.93) | 0.77 | (0.66, 0.89) | -0.06 | (-0.10,-0.03) | |
| Macroalbuminuria (>300) | 500 | 234 | 46.8 | 525 | 194 | 37.0 | 0.0013 | 0.79 | ( 0.68, 0.91) | 0.66 | (0.52, 0.85) | -0.10 | (-0.16,-0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0547 |
| Low, moderate or high | 2430 | 893 | 36.7 | 2495 | 742 | 29.7 | <0.0001 | 0.81 | ( 0.75, 0.88) | 0.73 | (0.65, 0.82) | -0.07 | (-0.10,-0.04) | |
| Very high | 834 | 379 | 45.4 | 820 | 345 | 42.1 | 0.1650 | 0.93 | ( 0.83, 1.03) | 0.87 | (0.72, 1.06) | -0.03 | (-0.08, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1226 |
| No | 572 | 241 | 42.1 | 578 | 226 | 39.1 | 0.2977 | 0.93 | ( 0.81, 1.07) | 0.88 | (0.70, 1.12) | -0.03 | (-0.09, 0.03) | |
| Yes | 2703 | 1035 | 38.3 | 2752 | 863 | 31.4 | <0.0001 | 0.82 | ( 0.76, 0.88) | 0.74 | (0.66, 0.82) | -0.07 | (-0.09,-0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4759 |
| No | 344 | 137 | 39.8 | 349 | 125 | 35.8 | 0.2643 | 0.90 | ( 0.74, 1.09) | 0.84 | (0.62, 1.14) | -0.04 | (-0.11, 0.03) | |
| Yes | 2931 | 1139 | 38.9 | 2981 | 964 | 32.3 | <0.0001 | 0.83 | ( 0.78, 0.89) | 0.75 | (0.68, 0.84) | -0.06 | (-0.09,-0.04) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.3530 |
| No | 275 | 90 | 32.7 | 307 | 75 | 24.4 | 0.0273 | 0.75 ( 0.58, 0.97) | 0.67 (0.46, 0.96) | -0.08 (-0.16,-0.01) | |
| Yes | 3000 | 1186 | 39.5 | 3023 | 1014 | 33.5 | <0.0001 | 0.85 ( 0.79, 0.91) | 0.77 (0.70, 0.86) | -0.06 (-0.08,-0.04) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 476 | 14.5 | 3330 | 476 | 14.3 | 0.7546 | 0.98 ( 0.87, 1.10) | 0.98 (0.85, 1.12) | 0.00 (-0.02, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 325 | 9.9 | 3330 | 252 | 7.6 | 0.0006 | 0.76 | ( 0.65, 0.89) | 0.74 | (0.62, 0.88) | -0.02 | (-0.04,-0.01) | |
| Study | | | | | | | | | | | | | | 0.3654 |
| 1245.110 | 2001 | 217 | 10.8 | 2052 | 178 | 8.7 | 0.0199 | 0.80 | ( 0.66, 0.97) | 0.78 | (0.63, 0.96) | -0.02 | (-0.04, 0.00) | |
| 1245.121 | 1274 | 108 | 8.5 | 1278 | 74 | 5.8 | 0.0084 | 0.68 | ( 0.51, 0.91) | 0.66 | (0.49, 0.90) | -0.03 | (-0.05,-0.01) | |
| Sex | | | | | | | | | | | | | | 0.9050 |
| Male | 2023 | 207 | 10.2 | 2068 | 160 | 7.7 | 0.0051 | 0.76 | ( 0.62, 0.92) | 0.73 | (0.59, 0.91) | -0.03 | (-0.04,-0.01) | |
| Female | 1252 | 118 | 9.4 | 1262 | 92 | 7.3 | 0.0499 | 0.77 | ( 0.59, >1.00) | 0.75 | (0.57, 1.00) | -0.02 | (-0.04, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.5906 |
| <65 | 766 | 80 | 10.4 | 705 | 52 | 7.4 | 0.0382 | 0.70 | ( 0.50, 0.98) | 0.68 | (0.47, 0.98) | -0.03 | (-0.06, 0.00) | |
| >=65 | 2509 | 245 | 9.8 | 2625 | 200 | 7.6 | 0.0065 | 0.78 | ( 0.65, 0.93) | 0.76 | (0.63, 0.93) | -0.02 | (-0.04,-0.01) | |
| Region | | | | | | | | | | | | | | 0.7267 |
| North America | 434 | 86 | 19.8 | 432 | 71 | 16.4 | 0.1936 | 0.83 | ( 0.62, 1.10) | 0.79 | (0.56, 1.12) | -0.03 | (-0.09, 0.02) | |
| Latin America | 931 | 92 | 9.9 | 944 | 69 | 7.3 | 0.0498 | 0.74 | ( 0.55, >1.00) | 0.72 | (0.52, 1.00) | -0.03 | (-0.05, 0.00) | |
| Europe | 1334 | 111 | 8.3 | 1361 | 76 | 5.6 | 0.0052 | 0.67 | ( 0.51, 0.89) | 0.65 | (0.48, 0.88) | -0.03 | (-0.05,-0.01) | |
| Asia | 405 | 17 | 4.2 | 413 | 16 | 3.9 | 0.7569 | 0.90 | ( 0.46, 1.75) | 0.90 | (0.45, 1.80) | 0.00 | (-0.03, 0.02) | |
| Other | 171 | 19 | 11.1 | 180 | 20 | 11.1 | 0.9218 | 0.97 | ( 0.54, 1.74) | 0.97 | (0.50, 1.88) | 0.00 | (-0.07, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5160 |
| Diabetic | 1739 | 193 | 11.1 | 1779 | 157 | 8.8 | 0.0223 | 0.79 | ( 0.65, 0.97) | 0.77 | (0.62, 0.96) | -0.02 | (-0.04, 0.00) | |
| Non-Diabetic | 1536 | 132 | 8.6 | 1551 | 95 | 6.1 | 0.0085 | 0.71 | ( 0.55, 0.92) | 0.69 | (0.53, 0.91) | -0.02 | (-0.04,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1665 |
| <30 | 1975 | 176 | 8.9 | 1930 | 117 | 6.1 | 0.0006 | 0.68 | ( 0.54, 0.85) | 0.66 | (0.51, 0.84) | -0.03 | (-0.05,-0.01) | |
| >=30 | 1300 | 149 | 11.5 | 1400 | 135 | 9.6 | 0.1338 | 0.85 | ( 0.68, 1.05) | 0.83 | (0.65, 1.06) | -0.02 | (-0.04, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5936 |
| <130 | 1684 | 169 | 10.0 | 1687 | 135 | 8.0 | 0.0357 | 0.79 | ( 0.64, 0.99) | 0.78 | (0.61, 0.98) | -0.02 | (-0.04, 0.00) | |
| >=130 | 1591 | 156 | 9.8 | 1643 | 117 | 7.1 | 0.0065 | 0.73 | ( 0.58, 0.92) | 0.71 | (0.55, 0.91) | -0.03 | (-0.05,-0.01) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9717 |
| <75 | 1653 | 192 | 11.6 | 1612 | 142 | 8.8 | 0.0073 | 0.76 | ( 0.62, 0.93) | 0.73 | (0.58, 0.92) | -0.03 | (-0.05,-0.01) | |
| 75 to <85 | 1005 | 87 | 8.7 | 1085 | 74 | 6.8 | 0.1188 | 0.79 | ( 0.59, 1.06) | 0.77 | (0.56, 1.07) | -0.02 | (-0.04, 0.00) | |
| >=85 | 617 | 46 | 7.5 | 633 | 36 | 5.7 | 0.2123 | 0.77 | ( 0.50, 1.17) | 0.75 | (0.48, 1.18) | -0.02 | (-0.04, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5457 |
| <30 | 250 | 63 | 25.2 | 263 | 57 | 21.7 | 0.4794 | 0.89 | ( 0.65, 1.22) | 0.86 | (0.57, 1.30) | -0.03 | (-0.10, 0.05) | |
| 30 to <45 | 898 | 107 | 11.9 | 909 | 78 | 8.6 | 0.0183 | 0.72 | ( 0.54, 0.95) | 0.69 | (0.51, 0.94) | -0.03 | (-0.06,-0.01) | |
| >=45 | 2126 | 155 | 7.3 | 2158 | 117 | 5.4 | 0.0113 | 0.74 | ( 0.59, 0.94) | 0.73 | (0.57, 0.93) | -0.02 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3464 |
| Normal (<30) | 1216 | 102 | 8.4 | 1243 | 78 | 6.3 | 0.0439 | 0.75 | ( 0.56, 0.99) | 0.73 | (0.54, 0.99) | -0.02 | (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 151 | 9.8 | 1546 | 106 | 6.9 | 0.0031 | 0.70 | ( 0.55, 0.89) | 0.68 | (0.52, 0.88) | -0.03 | (-0.05,-0.01) | |
| Macroalbuminuria (>300) | 500 | 70 | 14.0 | 525 | 68 | 13.0 | 0.6546 | 0.93 | ( 0.68, 1.27) | 0.92 | (0.64, 1.32) | -0.01 | (-0.05, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2693 |
| Low, moderate or high | 2430 | 184 | 7.6 | 2495 | 136 | 5.5 | 0.0023 | 0.72 | ( 0.58, 0.89) | 0.70 | (0.56, 0.88) | -0.02 | (-0.04,-0.01) | |
| Very high | 834 | 139 | 16.7 | 820 | 116 | 14.1 | 0.1753 | 0.86 | ( 0.68, 1.07) | 0.83 | (0.63, 1.09) | -0.02 | (-0.06, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.7503 |
| No | 572 | 67 | 11.7 | 578 | 54 | 9.3 | 0.1962 | 0.80 | ( 0.57, 1.12) | 0.78 | (0.53, 1.14) | -0.02 | (-0.06, 0.01) | |
| Yes | 2703 | 258 | 9.5 | 2752 | 198 | 7.2 | 0.0016 | 0.75 | ( 0.63, 0.90) | 0.73 | (0.60, 0.89) | -0.02 | (-0.04,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.2535 |
| No | 344 | 39 | 11.3 | 349 | 23 | 6.6 | 0.0279 | 0.58 | ( 0.35, 0.95) | 0.55 | (0.32, 0.94) | -0.05 | (-0.09,-0.01) | |
| Yes | 2931 | 286 | 9.8 | 2981 | 229 | 7.7 | 0.0041 | 0.78 | ( 0.66, 0.93) | 0.77 | (0.64, 0.92) | -0.02 | (-0.04,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.3116 |
| No | 275 | 20 | 7.3 | 307 | 12 | 3.9 | 0.0772 | 0.54 ( 0.27, 1.08) | 0.52 (0.25, 1.08) | -0.03 (-0.07, 0.00) | |
| Yes | 3000 | 305 | 10.2 | 3023 | 240 | 7.9 | 0.0024 | 0.78 ( 0.66, 0.92) | 0.76 (0.64, 0.91) | -0.02 (-0.04,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 216 | 6.6 | 3330 | 261 | 7.8 | 0.0537 | 1.19 (<1.00, 1.41) | 1.20 (1.00, 1.45) | 0.01 ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 195 | 6.0 | 3330 | 182 | 5.5 | 0.3780 | 0.92 ( 0.75, 1.11) | 0.91 (0.74, 1.12) | -0.01 (-0.02, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 193 | 5.9 | 3330 | 159 | 4.8 | 0.0398 | 0.81 | ( 0.66, 0.99) | 0.80 | (0.64, 0.99) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.7700 |
| 1245.110 | 2001 | 145 | 7.2 | 2052 | 118 | 5.8 | 0.0533 | 0.79 | ( 0.63, >1.00) | 0.78 | (0.61, 1.00) | -0.01 | (-0.03, 0.00) | |
| 1245.121 | 1274 | 48 | 3.8 | 1278 | 41 | 3.2 | 0.4412 | 0.85 | ( 0.57, 1.28) | 0.85 | (0.55, 1.29) | -0.01 | (-0.02, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.6113 |
| Male | 2023 | 121 | 6.0 | 2068 | 96 | 4.6 | 0.0540 | 0.78 | ( 0.60, 1.01) | 0.76 | (0.58, 1.01) | -0.01 | (-0.03, 0.00) | |
| Female | 1252 | 72 | 5.8 | 1262 | 63 | 5.0 | 0.3819 | 0.86 | ( 0.62, 1.20) | 0.86 | (0.61, 1.21) | -0.01 | (-0.03, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.1763 |
| <65 | 766 | 40 | 5.2 | 705 | 39 | 5.5 | 0.8207 | 1.05 | ( 0.68, 1.61) | 1.05 | (0.67, 1.66) | 0.00 | (-0.02, 0.03) | |
| >=65 | 2509 | 153 | 6.1 | 2625 | 120 | 4.6 | 0.0153 | 0.75 | ( 0.60, 0.95) | 0.74 | (0.58, 0.94) | -0.02 | (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | | 0.5254 |
| North America | 434 | 58 | 13.4 | 432 | 40 | 9.3 | 0.0555 | 0.69 | ( 0.47, 1.01) | 0.66 | (0.43, 1.01) | -0.04 | (-0.08, 0.00) | |
| Latin America | 931 | 40 | 4.3 | 944 | 33 | 3.5 | 0.3919 | 0.82 | ( 0.52, 1.29) | 0.81 | (0.51, 1.30) | -0.01 | (-0.03, 0.01) | |
| Europe | 1334 | 78 | 5.8 | 1361 | 63 | 4.6 | 0.1472 | 0.79 | ( 0.57, 1.09) | 0.78 | (0.55, 1.09) | -0.01 | (-0.03, 0.00) | |
| Asia | 405 | 10 | 2.5 | 413 | 11 | 2.7 | 0.8897 | 1.06 | ( 0.46, 2.47) | 1.06 | (0.45, 2.54) | 0.00 | (-0.02, 0.02) | |
| Other | 171 | 7 | 4.1 | 180 | 12 | 6.7 | 0.3137 | 1.59 | ( 0.64, 3.93) | 1.63 | (0.63, 4.27) | 0.02 | (-0.02, 0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8428 |
| Diabetic | 1739 | 119 | 6.8 | 1779 | 97 | 5.5 | 0.0797 | 0.79 | ( 0.61, 1.03) | 0.78 | (0.59, 1.03) | -0.01 | (-0.03, 0.00) | |
| Non-Diabetic | 1536 | 74 | 4.8 | 1551 | 62 | 4.0 | 0.2612 | 0.83 | ( 0.60, 1.15) | 0.82 | (0.58, 1.16) | -0.01 | (-0.02, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4024 |
| <30 | 1975 | 102 | 5.2 | 1930 | 74 | 3.8 | 0.0385 | 0.74 | ( 0.55, 0.99) | 0.72 | (0.53, 0.98) | -0.01 | (-0.03, 0.00) | |
| >=30 | 1300 | 91 | 7.0 | 1400 | 85 | 6.1 | 0.3627 | 0.88 | ( 0.66, 1.17) | 0.87 | (0.64, 1.18) | -0.01 | (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6096 |
| <130 | 1684 | 94 | 5.6 | 1687 | 81 | 4.8 | 0.2749 | 0.85 | ( 0.64, 1.14) | 0.84 | (0.62, 1.15) | -0.01 | (-0.02, 0.01) | |
| >=130 | 1591 | 99 | 6.2 | 1643 | 78 | 4.7 | 0.0688 | 0.77 | ( 0.57, 1.02) | 0.75 | (0.56, 1.02) | -0.01 | (-0.03, 0.00) | |

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Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.8570 |
| <75 | 1653 | 95 | 5.7 | 1612 | 80 | 5.0 | 0.2931 | 0.86 | ( 0.64, 1.14) | 0.85 | (0.62, 1.15) | -0.01 | (-0.02, 0.01) | |
| 75 to <85 | 1005 | 62 | 6.2 | 1085 | 51 | 4.7 | 0.1421 | 0.76 | ( 0.53, 1.10) | 0.75 | (0.51, 1.10) | -0.01 | (-0.03, 0.00) | |
| >=85 | 617 | 36 | 5.8 | 633 | 28 | 4.4 | 0.2641 | 0.76 | ( 0.47, 1.23) | 0.75 | (0.45, 1.24) | -0.01 | (-0.04, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5576 |
| <30 | 250 | 21 | 8.4 | 263 | 21 | 8.0 | 0.9468 | 1.02 | ( 0.57, 1.84) | 1.02 | (0.54, 1.94) | 0.00 | (-0.05, 0.05) | |
| 30 to <45 | 898 | 56 | 6.2 | 909 | 50 | 5.5 | 0.4868 | 0.88 | ( 0.61, 1.27) | 0.87 | (0.59, 1.29) | -0.01 | (-0.03, 0.01) | |
| >=45 | 2126 | 116 | 5.5 | 2158 | 88 | 4.1 | 0.0301 | 0.74 | ( 0.57, 0.97) | 0.73 | (0.55, 0.97) | -0.01 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9670 |
| Normal (<30) | 1216 | 66 | 5.4 | 1243 | 56 | 4.5 | 0.2827 | 0.83 | ( 0.59, 1.17) | 0.82 | (0.57, 1.18) | -0.01 | (-0.03, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 83 | 5.4 | 1546 | 69 | 4.5 | 0.2281 | 0.83 | ( 0.61, 1.13) | 0.82 | (0.59, 1.13) | -0.01 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 500 | 42 | 8.4 | 525 | 34 | 6.5 | 0.2489 | 0.77 | ( 0.50, 1.20) | 0.76 | (0.47, 1.21) | -0.02 | (-0.05, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0727 |
| Low, moderate or high | 2430 | 136 | 5.6 | 2495 | 101 | 4.0 | 0.0096 | 0.72 | ( 0.56, 0.92) | 0.71 | (0.54, 0.92) | -0.02 | (-0.03, 0.00) | |
| Very high | 834 | 56 | 6.7 | 820 | 58 | 7.1 | 0.7113 | 1.07 | ( 0.75, 1.52) | 1.08 | (0.73, 1.58) | 0.00 | (-0.02, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4514 |
| No | 572 | 44 | 7.7 | 578 | 41 | 7.1 | 0.7203 | 0.93 | ( 0.62, 1.40) | 0.92 | (0.59, 1.44) | -0.01 | (-0.04, 0.02) | |
| Yes | 2703 | 149 | 5.5 | 2752 | 118 | 4.3 | 0.0329 | 0.77 | ( 0.61, 0.98) | 0.76 | (0.60, 0.98) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.8545 |
| No | 344 | 27 | 7.8 | 349 | 21 | 6.0 | 0.3509 | 0.77 | ( 0.44, 1.34) | 0.75 | (0.42, 1.36) | -0.02 | (-0.06, 0.02) | |
| Yes | 2931 | 166 | 5.7 | 2981 | 138 | 4.6 | 0.0641 | 0.81 | ( 0.65, 1.01) | 0.80 | (0.64, 1.01) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.9848 |
| No | 275 | 11 | 4.0 | 307 | 10 | 3.3 | 0.6313 | 0.82 ( 0.36, 1.87) | 0.81 (0.35, 1.91) | -0.01 (-0.04, 0.02) | |
| Yes | 3000 | 182 | 6.1 | 3023 | 149 | 4.9 | 0.0485 | 0.81 ( 0.66, <1.00) | 0.80 (0.64, 1.00) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 192 | 5.9 | 3330 | 193 | 5.8 | 0.9010 | 0.99 ( 0.81, 1.20) | 0.99 (0.80, 1.21) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 143 | 4.4 | 3330 | 174 | 5.2 | 0.1064 | 1.19 ( 0.96, 1.48) | 1.21 (0.96, 1.51) | 0.01 ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 161 | 4.9 | 3330 | 169 | 5.1 | 0.7926 | 1.03 | ( 0.83, 1.27) | 1.03 | (0.83, 1.29) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 165 | 5.0 | 3330 | 123 | 3.7 | 0.0071 | 0.73 | ( 0.58, 0.92) | 0.72 | (0.57, 0.92) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.9145 |
| 1245.110 | 2001 | 115 | 5.7 | 2052 | 87 | 4.2 | 0.0275 | 0.74 | ( 0.56, 0.97) | 0.73 | (0.55, 0.97) | -0.02 | (-0.03, 0.00) | |
| 1245.121 | 1274 | 50 | 3.9 | 1278 | 36 | 2.8 | 0.1211 | 0.72 | ( 0.47, 1.09) | 0.71 | (0.46, 1.10) | -0.01 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4294 |
| Male | 2023 | 105 | 5.2 | 2068 | 73 | 3.5 | 0.0091 | 0.68 | ( 0.51, 0.91) | 0.67 | (0.49, 0.91) | -0.02 | (-0.03, 0.00) | |
| Female | 1252 | 60 | 4.8 | 1262 | 50 | 4.0 | 0.2900 | 0.82 | ( 0.57, 1.18) | 0.81 | (0.55, 1.19) | -0.01 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.5255 |
| <65 | 766 | 40 | 5.2 | 705 | 31 | 4.4 | 0.4390 | 0.84 | ( 0.53, 1.32) | 0.83 | (0.51, 1.34) | -0.01 | (-0.03, 0.01) | |
| >=65 | 2509 | 125 | 5.0 | 2625 | 92 | 3.5 | 0.0087 | 0.70 | ( 0.54, 0.92) | 0.69 | (0.53, 0.91) | -0.01 | (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | | 0.3834 |
| North America | 434 | 38 | 8.8 | 432 | 33 | 7.6 | 0.5478 | 0.87 | ( 0.56, 1.36) | 0.86 | (0.53, 1.40) | -0.01 | (-0.05, 0.03) | |
| Latin America | 931 | 46 | 4.9 | 944 | 39 | 4.1 | 0.4270 | 0.84 | ( 0.56, 1.28) | 0.84 | (0.54, 1.30) | -0.01 | (-0.03, 0.01) | |
| Europe | 1334 | 52 | 3.9 | 1361 | 28 | 2.1 | 0.0049 | 0.53 | ( 0.34, 0.83) | 0.52 | (0.33, 0.83) | -0.02 | (-0.03,-0.01) | |
| Asia | 405 | 17 | 4.2 | 413 | 10 | 2.4 | 0.1405 | 0.57 | ( 0.26, 1.22) | 0.55 | (0.25, 1.23) | -0.02 | (-0.04, 0.01) | |
| Other | 171 | 12 | 7.0 | 180 | 13 | 7.2 | 0.9741 | 1.01 | ( 0.48, 2.15) | 1.01 | (0.45, 2.26) | 0.00 | (-0.05, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6422 |
| Diabetic | 1739 | 119 | 6.8 | 1779 | 92 | 5.2 | 0.0351 | 0.75 | ( 0.58, 0.98) | 0.74 | (0.56, 0.98) | -0.02 | (-0.03, 0.00) | |
| Non-Diabetic | 1536 | 46 | 3.0 | 1551 | 31 | 2.0 | 0.0748 | 0.67 | ( 0.42, 1.04) | 0.66 | (0.42, 1.05) | -0.01 | (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1528 |
| <30 | 1975 | 95 | 4.8 | 1930 | 58 | 3.0 | 0.0032 | 0.62 | ( 0.45, 0.86) | 0.61 | (0.44, 0.85) | -0.02 | (-0.03,-0.01) | |
| >=30 | 1300 | 70 | 5.4 | 1400 | 65 | 4.6 | 0.3998 | 0.87 | ( 0.63, 1.21) | 0.86 | (0.61, 1.22) | -0.01 | (-0.02, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.0900 |
| <130 | 1684 | 91 | 5.4 | 1687 | 55 | 3.3 | 0.0020 | 0.60 | ( 0.43, 0.83) | 0.59 | (0.42, 0.83) | -0.02 | (-0.04,-0.01) | |
| >=130 | 1591 | 74 | 4.7 | 1643 | 68 | 4.1 | 0.4911 | 0.89 | ( 0.65, 1.23) | 0.89 | (0.63, 1.24) | 0.00 | (-0.02, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6273 |
| <75 | 1653 | 96 | 5.8 | 1612 | 63 | 3.9 | 0.0106 | 0.67 | ( 0.49, 0.91) | 0.66 | (0.47, 0.91) | -0.02 | (-0.03, 0.00) | |
| 75 to <85 | 1005 | 44 | 4.4 | 1085 | 37 | 3.4 | 0.2568 | 0.78 | ( 0.51, 1.20) | 0.77 | (0.49, 1.21) | -0.01 | (-0.03, 0.01) | |
| >=85 | 617 | 25 | 4.1 | 633 | 23 | 3.6 | 0.7064 | 0.90 | ( 0.52, 1.57) | 0.89 | (0.50, 1.59) | 0.00 | (-0.03, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0049 |
| <30 | 250 | 15 | 6.0 | 263 | 28 | 10.6 | 0.0470 | 1.84 | (<1.00, 3.38) | 1.94 | (1.00, 3.75) | 0.05 | ( 0.00, 0.10) | |
| 30 to <45 | 898 | 59 | 6.6 | 909 | 34 | 3.7 | 0.0062 | 0.57 | ( 0.38, 0.86) | 0.55 | (0.36, 0.85) | -0.03 | (-0.05,-0.01) | |
| >=45 | 2126 | 91 | 4.3 | 2158 | 61 | 2.8 | 0.0090 | 0.66 | ( 0.48, 0.90) | 0.65 | (0.46, 0.90) | -0.01 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.0475 |
| Normal (<30) | 1216 | 55 | 4.5 | 1243 | 28 | 2.3 | 0.0018 | 0.50 | ( 0.32, 0.78) | 0.49 | (0.31, 0.77) | -0.02 | (-0.04,-0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 77 | 5.0 | 1546 | 57 | 3.7 | 0.0747 | 0.74 | ( 0.53, 1.03) | 0.73 | (0.51, 1.03) | -0.01 | (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 500 | 33 | 6.6 | 525 | 38 | 7.2 | 0.6611 | 1.11 | ( 0.71, 1.73) | 1.11 | (0.69, 1.81) | 0.01 | (-0.02, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.0600 |
| Low, moderate or high | 2430 | 104 | 4.3 | 2495 | 66 | 2.6 | 0.0015 | 0.62 | ( 0.45, 0.83) | 0.60 | (0.44, 0.83) | -0.02 | (-0.03,-0.01) | |
| Very high | 834 | 61 | 7.3 | 820 | 57 | 7.0 | 0.8078 | 0.96 | ( 0.68, 1.36) | 0.95 | (0.66, 1.39) | 0.00 | (-0.03, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.9227 |
| No | 572 | 36 | 6.3 | 578 | 26 | 4.5 | 0.1805 | 0.72 | ( 0.44, 1.17) | 0.70 | (0.42, 1.18) | -0.02 | (-0.04, 0.01) | |
| Yes | 2703 | 129 | 4.8 | 2752 | 97 | 3.5 | 0.0194 | 0.74 | ( 0.57, 0.95) | 0.73 | (0.55, 0.95) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9711 |
| No | 344 | 15 | 4.4 | 349 | 11 | 3.2 | 0.3938 | 0.72 | ( 0.34, 1.54) | 0.71 | (0.32, 1.57) | -0.01 | (-0.04, 0.02) | |
| Yes | 2931 | 150 | 5.1 | 2981 | 112 | 3.8 | 0.0100 | 0.73 | ( 0.58, 0.93) | 0.72 | (0.56, 0.93) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.6013 |
| No | 275 | 11 | 4.0 | 307 | 11 | 3.6 | 0.7999 | 0.90 ( 0.40, 2.02) | 0.90 (0.39, 2.07) | 0.00 (-0.04, 0.03) | |
| Yes | 3000 | 154 | 5.1 | 3023 | 112 | 3.7 | 0.0066 | 0.72 ( 0.57, 0.91) | 0.71 (0.55, 0.91) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 162 | 4.9 | 3330 | 147 | 4.4 | 0.2946 | 0.89 ( 0.72, 1.11) | 0.88 (0.70, 1.11) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 76 | 2.3 | 3330 | 60 | 1.8 | 0.1360 | 0.78 ( 0.55, 1.08) | 0.77 (0.55, 1.09) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 74 | 2.3 | 3330 | 45 | 1.4 | 0.0051 | 0.60 | ( 0.41, 0.86) | 0.59 | (0.41, 0.86) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.3862 |
| 1245.110 | 2001 | 62 | 3.1 | 2052 | 35 | 1.7 | 0.0037 | 0.55 | ( 0.37, 0.83) | 0.54 | (0.36, 0.83) | -0.01 | (-0.02, 0.00) | |
| 1245.121 | 1274 | 12 | 0.9 | 1278 | 10 | 0.8 | 0.6632 | 0.83 | ( 0.36, 1.92) | 0.83 | (0.36, 1.93) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.4113 |
| Male | 2023 | 42 | 2.1 | 2068 | 29 | 1.4 | 0.0969 | 0.67 | ( 0.42, 1.08) | 0.67 | (0.41, 1.08) | -0.01 | (-0.01, 0.00) | |
| Female | 1252 | 32 | 2.6 | 1262 | 16 | 1.3 | 0.0164 | 0.49 | ( 0.27, 0.89) | 0.48 | (0.26, 0.89) | -0.01 | (-0.02, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.4529 |
| <65 | 766 | 11 | 1.4 | 705 | 4 | 0.6 | 0.0946 | 0.39 | ( 0.13, 1.22) | 0.39 | (0.12, 1.23) | -0.01 | (-0.02, 0.00) | |
| >=65 | 2509 | 63 | 2.5 | 2625 | 41 | 1.6 | 0.0163 | 0.62 | ( 0.42, 0.92) | 0.62 | (0.41, 0.92) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | 0.6329 |
| North America | 434 | 18 | 4.1 | 432 | 12 | 2.8 | 0.2690 | 0.67 | ( 0.33, 1.37) | 0.66 | (0.31, 1.39) | -0.01 | (-0.04, 0.01) | |
| Latin America | 931 | 9 | 1.0 | 944 | 6 | 0.6 | 0.4583 | 0.69 | ( 0.25, 1.86) | 0.68 | (0.25, 1.87) | 0.00 | (-0.01, 0.01) | |
| Europe | 1334 | 34 | 2.5 | 1361 | 18 | 1.3 | 0.0193 | 0.52 | ( 0.29, 0.91) | 0.51 | (0.29, 0.91) | -0.01 | (-0.02, 0.00) | |
| Asia | 405 | 9 | 2.2 | 413 | 9 | 2.2 | 0.9257 | 0.96 | ( 0.38, 2.38) | 0.96 | (0.38, 2.44) | 0.00 | (-0.02, 0.02) | |
| Other | 171 | 4 | 2.3 | 180 | 0 | 0 | 0.0837 | 0.19 | ( 0.02, 1.57) | 0.19 | (0.02, 1.59) | -0.02 | (-0.05, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2600 |
| Diabetic | 1739 | 33 | 1.9 | 1779 | 25 | 1.4 | 0.2419 | 0.74 | ( 0.44, 1.23) | 0.73 | (0.43, 1.24) | -0.01 | (-0.01, 0.00) | |
| Non-Diabetic | 1536 | 41 | 2.7 | 1551 | 20 | 1.3 | 0.0056 | 0.48 | ( 0.28, 0.82) | 0.47 | (0.28, 0.81) | -0.01 | (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.5626 |
| <30 | 1975 | 45 | 2.3 | 1930 | 29 | 1.5 | 0.0632 | 0.65 | ( 0.41, 1.03) | 0.64 | (0.40, 1.03) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1300 | 29 | 2.2 | 1400 | 16 | 1.1 | 0.0302 | 0.52 | ( 0.28, 0.95) | 0.51 | (0.28, 0.95) | -0.01 | (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8129 |
| <130 | 1684 | 38 | 2.3 | 1687 | 22 | 1.3 | 0.0306 | 0.57 | ( 0.34, 0.96) | 0.56 | (0.33, 0.95) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1591 | 36 | 2.3 | 1643 | 23 | 1.4 | 0.0695 | 0.62 | ( 0.37, 1.04) | 0.62 | (0.36, 1.04) | -0.01 | (-0.02, 0.00) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6125 |
| <75 | 1653 | 41 | 2.5 | 1612 | 22 | 1.4 | 0.0176 | 0.54 | ( 0.33, 0.91) | 0.54 | (0.32, 0.90) | -0.01 | (-0.02, 0.00) | |
| 75 to <85 | 1005 | 19 | 1.9 | 1085 | 16 | 1.5 | 0.4682 | 0.78 | ( 0.41, 1.51) | 0.78 | (0.40, 1.53) | 0.00 | (-0.02, 0.01) | |
| >=85 | 617 | 14 | 2.3 | 633 | 7 | 1.1 | 0.1115 | 0.49 | ( 0.20, 1.20) | 0.48 | (0.19, 1.20) | -0.01 | (-0.03, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.4111 |
| <30 | 250 | 11 | 4.4 | 263 | 8 | 3.0 | 0.5499 | 0.76 | ( 0.31, 1.86) | 0.75 | (0.30, 1.92) | -0.01 | (-0.04, 0.02) | |
| 30 to <45 | 898 | 23 | 2.6 | 909 | 18 | 2.0 | 0.3930 | 0.77 | ( 0.42, 1.41) | 0.76 | (0.41, 1.42) | -0.01 | (-0.02, 0.01) | |
| >=45 | 2126 | 40 | 1.9 | 2158 | 19 | 0.9 | 0.0043 | 0.46 | ( 0.27, 0.80) | 0.46 | (0.26, 0.79) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.4775 |
| Normal (<30) | 1216 | 23 | 1.9 | 1243 | 15 | 1.2 | 0.1641 | 0.64 | ( 0.33, 1.21) | 0.63 | (0.33, 1.21) | -0.01 | (-0.02, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 36 | 2.3 | 1546 | 25 | 1.6 | 0.1436 | 0.69 | ( 0.42, 1.14) | 0.68 | (0.41, 1.14) | -0.01 | (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 500 | 14 | 2.8 | 525 | 5 | 1.0 | 0.0298 | 0.34 | ( 0.12, 0.95) | 0.34 | (0.12, 0.94) | -0.02 | (-0.03, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2543 |
| Low, moderate or high | 2430 | 46 | 1.9 | 2495 | 24 | 1.0 | 0.0049 | 0.50 | ( 0.31, 0.82) | 0.50 | (0.30, 0.82) | -0.01 | (-0.02, 0.00) | |
| Very high | 834 | 28 | 3.4 | 820 | 21 | 2.6 | 0.3651 | 0.77 | ( 0.44, 1.35) | 0.77 | (0.43, 1.36) | -0.01 | (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3861 |
| No | 572 | 18 | 3.1 | 578 | 14 | 2.4 | 0.4650 | 0.77 | ( 0.39, 1.54) | 0.77 | (0.38, 1.56) | -0.01 | (-0.03, 0.01) | |
| Yes | 2703 | 56 | 2.1 | 2752 | 31 | 1.1 | 0.0047 | 0.54 | ( 0.35, 0.83) | 0.53 | (0.34, 0.83) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.5781 |
| No | 344 | 15 | 4.4 | 349 | 7 | 2.0 | 0.0852 | 0.48 | ( 0.20, 1.13) | 0.47 | (0.19, 1.13) | -0.02 | (-0.05, 0.00) | |
| Yes | 2931 | 59 | 2.0 | 2981 | 38 | 1.3 | 0.0228 | 0.63 | ( 0.42, 0.94) | 0.62 | (0.41, 0.94) | -0.01 | (-0.01, 0.00) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

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System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.9543 |
| No | 275 | 6 | 2.2 | 307 | 4 | 1.3 | 0.4279 | 0.62 ( 0.19, 2.05) | 0.61 (0.18, 2.07) | -0.01 (-0.03, 0.01) | |
| Yes | 3000 | 68 | 2.3 | 3023 | 41 | 1.4 | 0.0074 | 0.60 ( 0.41, 0.87) | 0.59 (0.40, 0.87) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 72 | 2.2 | 3330 | 62 | 1.9 | 0.3242 | 0.84 ( 0.60, 1.18) | 0.84 (0.60, 1.19) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 44 | 1.3 | 3330 | 48 | 1.4 | 0.7459 | 1.07 ( 0.71, 1.60) | 1.07 (0.71, 1.62) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 27 | 0.8 | 3330 | 37 | 1.1 | 0.2385 | 1.34 ( 0.82, 2.20) | 1.35 (0.82, 2.22) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 26 | 0.8 | 3330 | 34 | 1.0 | 0.3287 | 1.29 ( 0.77, 2.14) | 1.29 (0.77, 2.15) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 627 | 19.1 | 3330 | 529 | 15.9 | 0.0005 | 0.83 | ( 0.75, 0.92) | 0.80 | (0.70, 0.91) | -0.03 | (-0.05,-0.01) | |
| Study | | | | | | | | | | | | | | 0.7603 |
| 1245.110 | 2001 | 362 | 18.1 | 2052 | 304 | 14.8 | 0.0049 | 0.82 | ( 0.71, 0.94) | 0.79 | (0.67, 0.93) | -0.03 | (-0.06,-0.01) | |
| 1245.121 | 1274 | 265 | 20.8 | 1278 | 225 | 17.6 | 0.0405 | 0.85 | ( 0.72, 0.99) | 0.81 | (0.67, 0.99) | -0.03 | (-0.06, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.1111 |
| Male | 2023 | 399 | 19.7 | 2068 | 360 | 17.4 | 0.0574 | 0.88 | ( 0.78,>1.00) | 0.86 | (0.73, 1.00) | -0.02 | (-0.05, 0.00) | |
| Female | 1252 | 228 | 18.2 | 1262 | 169 | 13.4 | 0.0010 | 0.74 | ( 0.61, 0.88) | 0.70 | (0.56, 0.86) | -0.05 | (-0.08,-0.02) | |
| Age [years] | | | | | | | | | | | | | | 0.5899 |
| <65 | 766 | 164 | 21.4 | 705 | 119 | 16.9 | 0.0297 | 0.79 | ( 0.64, 0.98) | 0.75 | (0.57, 0.97) | -0.04 | (-0.08, 0.00) | |
| >=65 | 2509 | 463 | 18.5 | 2625 | 410 | 15.6 | 0.0068 | 0.85 | ( 0.75, 0.96) | 0.82 | (0.71, 0.95) | -0.03 | (-0.05,-0.01) | |
| Region | | | | | | | | | | | | | | 0.8984 |
| North America | 434 | 119 | 27.4 | 432 | 107 | 24.8 | 0.3772 | 0.90 | ( 0.72, 1.13) | 0.87 | (0.64, 1.18) | -0.03 | (-0.08, 0.03) | |
| Latin America | 931 | 184 | 19.8 | 944 | 158 | 16.7 | 0.0905 | 0.85 | ( 0.70, 1.03) | 0.82 | (0.65, 1.03) | -0.03 | (-0.07, 0.00) | |
| Europe | 1334 | 218 | 16.3 | 1361 | 175 | 12.9 | 0.0109 | 0.79 | ( 0.66, 0.95) | 0.76 | (0.61, 0.94) | -0.03 | (-0.06,-0.01) | |
| Asia | 405 | 78 | 19.3 | 413 | 67 | 16.2 | 0.2792 | 0.85 | ( 0.63, 1.14) | 0.82 | (0.57, 1.18) | -0.03 | (-0.08, 0.02) | |
| Other | 171 | 28 | 16.4 | 180 | 22 | 12.2 | 0.2680 | 0.75 | ( 0.44, 1.25) | 0.71 | (0.39, 1.30) | -0.04 | (-0.11, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2012 |
| Diabetic | 1739 | 376 | 21.6 | 1779 | 301 | 16.9 | 0.0004 | 0.78 | ( 0.68, 0.90) | 0.74 | (0.62, 0.87) | -0.05 | (-0.07,-0.02) | |
| Non-Diabetic | 1536 | 251 | 16.3 | 1551 | 228 | 14.7 | 0.2112 | 0.90 | ( 0.76, 1.06) | 0.88 | (0.73, 1.07) | -0.02 | (-0.04, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8573 |
| <30 | 1975 | 385 | 19.5 | 1930 | 309 | 16.0 | 0.0046 | 0.82 | ( 0.72, 0.94) | 0.79 | (0.67, 0.93) | -0.03 | (-0.06,-0.01) | |
| >=30 | 1300 | 242 | 18.6 | 1400 | 220 | 15.7 | 0.0369 | 0.84 | ( 0.71, 0.99) | 0.81 | (0.66, 0.99) | -0.03 | (-0.06, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.2410 |
| <130 | 1684 | 347 | 20.6 | 1687 | 305 | 18.1 | 0.0701 | 0.88 | ( 0.77, 1.01) | 0.85 | (0.72, 1.01) | -0.02 | (-0.05, 0.00) | |
| >=130 | 1591 | 280 | 17.6 | 1643 | 224 | 13.6 | 0.0019 | 0.78 | ( 0.66, 0.91) | 0.74 | (0.61, 0.90) | -0.04 | (-0.06,-0.01) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.6040 |
| <75 | 1653 | 339 | 20.5 | 1612 | 287 | 17.8 | 0.0532 | 0.87 | ( 0.76,>1.00) | 0.84 | (0.71, 1.00) | -0.03 | (-0.05, 0.00) | |
| 75 to <85 | 1005 | 184 | 18.3 | 1085 | 162 | 14.9 | 0.0374 | 0.82 | ( 0.67, 0.99) | 0.78 | (0.62, 0.99) | -0.03 | (-0.07, 0.00) | |
| >=85 | 617 | 104 | 16.9 | 633 | 80 | 12.6 | 0.0347 | 0.75 | ( 0.57, 0.98) | 0.71 | (0.52, 0.98) | -0.04 | (-0.08, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5131 |
| <30 | 250 | 73 | 29.2 | 263 | 68 | 25.9 | 0.4642 | 0.90 | ( 0.68, 1.19) | 0.86 | (0.58, 1.28) | -0.03 | (-0.11, 0.05) | |
| 30 to <45 | 898 | 183 | 20.4 | 909 | 165 | 18.2 | 0.2317 | 0.89 | ( 0.74, 1.08) | 0.87 | (0.69, 1.10) | -0.02 | (-0.06, 0.01) | |
| >=45 | 2126 | 371 | 17.5 | 2158 | 296 | 13.7 | 0.0009 | 0.79 | ( 0.69, 0.91) | 0.76 | (0.64, 0.89) | -0.04 | (-0.06,-0.02) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5213 |
| Normal (<30) | 1216 | 202 | 16.6 | 1243 | 171 | 13.8 | 0.0490 | 0.83 | ( 0.69,<1.00) | 0.80 | (0.64, 1.00) | -0.03 | (-0.06, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 294 | 19.0 | 1546 | 256 | 16.6 | 0.0826 | 0.87 | ( 0.75, 1.02) | 0.85 | (0.71, 1.02) | -0.02 | (-0.05, 0.00) | |
| Macroalbuminuria (>300) | 500 | 129 | 25.8 | 525 | 101 | 19.2 | 0.0116 | 0.74 | ( 0.59, 0.94) | 0.68 | (0.51, 0.92) | -0.07 | (-0.12,-0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5506 |
| Low, moderate or high | 2430 | 416 | 17.1 | 2495 | 349 | 14.0 | 0.0028 | 0.82 | ( 0.72, 0.93) | 0.79 | (0.68, 0.92) | -0.03 | (-0.05,-0.01) | |
| Very high | 834 | 209 | 25.1 | 820 | 180 | 22.0 | 0.1360 | 0.88 | ( 0.74, 1.04) | 0.84 | (0.67, 1.06) | -0.03 | (-0.07, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1916 |
| No | 572 | 116 | 20.3 | 578 | 112 | 19.4 | 0.6991 | 0.96 | ( 0.76, 1.21) | 0.94 | (0.71, 1.26) | -0.01 | (-0.06, 0.04) | |
| Yes | 2703 | 511 | 18.9 | 2752 | 417 | 15.2 | 0.0002 | 0.80 | ( 0.71, 0.90) | 0.77 | (0.67, 0.88) | -0.04 | (-0.06,-0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.6532 |
| No | 344 | 67 | 19.5 | 349 | 61 | 17.5 | 0.4552 | 0.89 | ( 0.65, 1.21) | 0.86 | (0.59, 1.27) | -0.02 | (-0.08, 0.04) | |
| Yes | 2931 | 560 | 19.1 | 2981 | 468 | 15.7 | 0.0006 | 0.82 | ( 0.74, 0.92) | 0.79 | (0.69, 0.90) | -0.03 | (-0.05,-0.01) | |

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MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.9397 |
| No | 275 | 35 | 12.7 | 307 | 32 | 10.4 | 0.3847 | 0.82 ( 0.52, 1.28) | 0.80 (0.48, 1.33) | -0.02 (-0.08, 0.03) | |
| Yes | 3000 | 592 | 19.7 | 3023 | 497 | 16.4 | 0.0009 | 0.83 ( 0.75, 0.93) | 0.80 (0.70, 0.91) | -0.03 (-0.05,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 266 | 8.1 | 3330 | 293 | 8.8 | 0.3333 | 1.08 ( 0.92, 1.27) | 1.09 (0.92, 1.30) | 0.01 (-0.01, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 174 | 5.3 | 3330 | 140 | 4.2 | 0.0330 | 0.79 | ( 0.64, 0.98) | 0.78 | (0.62, 0.98) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.7588 |
| 1245.110 | 2001 | 120 | 6.0 | 2052 | 95 | 4.6 | 0.0522 | 0.77 | ( 0.59,>1.00) | 0.76 | (0.58, 1.00) | -0.01 | (-0.03, 0.00) | |
| 1245.121 | 1274 | 54 | 4.2 | 1278 | 45 | 3.5 | 0.3481 | 0.83 | ( 0.56, 1.22) | 0.82 | (0.55, 1.23) | -0.01 | (-0.02, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.8470 |
| Male | 2023 | 111 | 5.5 | 2068 | 91 | 4.4 | 0.1078 | 0.80 | ( 0.61, 1.05) | 0.79 | (0.60, 1.05) | -0.01 | (-0.02, 0.00) | |
| Female | 1252 | 63 | 5.0 | 1262 | 49 | 3.9 | 0.1523 | 0.77 | ( 0.53, 1.10) | 0.76 | (0.52, 1.11) | -0.01 | (-0.03, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.2201 |
| <65 | 766 | 41 | 5.4 | 705 | 38 | 5.4 | 0.9932 | 1.00 | ( 0.65, 1.54) | 1.00 | (0.64, 1.58) | 0.00 | (-0.02, 0.02) | |
| >=65 | 2509 | 133 | 5.3 | 2625 | 102 | 3.9 | 0.0156 | 0.73 | ( 0.57, 0.94) | 0.72 | (0.55, 0.94) | -0.01 | (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | | 0.9541 |
| North America | 434 | 40 | 9.2 | 432 | 33 | 7.6 | 0.4030 | 0.83 | ( 0.53, 1.29) | 0.81 | (0.50, 1.32) | -0.02 | (-0.05, 0.02) | |
| Latin America | 931 | 59 | 6.3 | 944 | 51 | 5.4 | 0.4155 | 0.86 | ( 0.60, 1.24) | 0.85 | (0.58, 1.25) | -0.01 | (-0.03, 0.01) | |
| Europe | 1334 | 54 | 4.0 | 1361 | 38 | 2.8 | 0.0740 | 0.69 | ( 0.46, 1.04) | 0.68 | (0.45, 1.04) | -0.01 | (-0.03, 0.00) | |
| Asia | 405 | 12 | 3.0 | 413 | 10 | 2.4 | 0.5735 | 0.79 | ( 0.35, 1.80) | 0.78 | (0.33, 1.84) | -0.01 | (-0.03, 0.02) | |
| Other | 171 | 9 | 5.3 | 180 | 8 | 4.4 | 0.6809 | 0.83 | ( 0.34, 2.04) | 0.82 | (0.31, 2.13) | -0.01 | (-0.06, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0426 |
| Diabetic | 1739 | 101 | 5.8 | 1779 | 97 | 5.5 | 0.6344 | 0.94 | ( 0.71, 1.23) | 0.93 | (0.70, 1.24) | 0.00 | (-0.02, 0.01) | |
| Non-Diabetic | 1536 | 73 | 4.8 | 1551 | 43 | 2.8 | 0.0038 | 0.58 | ( 0.40, 0.84) | 0.57 | (0.39, 0.84) | -0.02 | (-0.03,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7681 |
| <30 | 1975 | 83 | 4.2 | 1930 | 66 | 3.4 | 0.1999 | 0.81 | ( 0.59, 1.12) | 0.81 | (0.58, 1.12) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1300 | 91 | 7.0 | 1400 | 74 | 5.3 | 0.0715 | 0.76 | ( 0.57, 1.02) | 0.75 | (0.54, 1.03) | -0.02 | (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9333 |
| <130 | 1684 | 86 | 5.1 | 1687 | 69 | 4.1 | 0.1540 | 0.80 | ( 0.59, 1.09) | 0.79 | (0.57, 1.09) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1591 | 88 | 5.5 | 1643 | 71 | 4.3 | 0.1169 | 0.78 | ( 0.58, 1.06) | 0.77 | (0.56, 1.07) | -0.01 | (-0.03, 0.00) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

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System organ class: Renal and urinary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk ratio (95% CI) | Odds ratio | Odds ratio (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.9965 |
| <75 | 1653 | 101 | 6.1 | 1612 | 78 | 4.8 | 0.1055 | 0.79 | ( 0.59, 1.05) | 0.78 | (0.57, 1.05) | -0.01 | (-0.03, 0.00) | |
| 75 to <85 | 1005 | 45 | 4.5 | 1085 | 39 | 3.6 | 0.3092 | 0.80 | ( 0.53, 1.23) | 0.80 | (0.51, 1.23) | -0.01 | (-0.03, 0.01) | |
| >=85 | 617 | 28 | 4.5 | 633 | 23 | 3.6 | 0.4271 | 0.80 | ( 0.47, 1.38) | 0.80 | (0.45, 1.40) | -0.01 | (-0.03, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5588 |
| <30 | 250 | 46 | 18.4 | 263 | 42 | 16.0 | 0.6336 | 0.91 | ( 0.62, 1.34) | 0.89 | (0.56, 1.42) | -0.02 | (-0.08, 0.05) | |
| 30 to <45 | 898 | 54 | 6.0 | 909 | 46 | 5.1 | 0.3668 | 0.84 | ( 0.57, 1.23) | 0.83 | (0.55, 1.24) | -0.01 | (-0.03, 0.01) | |
| >=45 | 2126 | 74 | 3.5 | 2158 | 52 | 2.4 | 0.0379 | 0.69 | ( 0.49, 0.98) | 0.68 | (0.48, 0.98) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.2986 |
| Normal (<30) | 1216 | 51 | 4.2 | 1243 | 41 | 3.3 | 0.2408 | 0.79 | ( 0.52, 1.18) | 0.78 | (0.51, 1.18) | -0.01 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 72 | 4.7 | 1546 | 47 | 3.0 | 0.0190 | 0.65 | ( 0.45, 0.93) | 0.64 | (0.44, 0.93) | -0.02 | (-0.03, 0.00) | |
| Macroalbuminuria (>300) | 500 | 51 | 10.2 | 525 | 52 | 9.9 | 0.9110 | 0.98 | ( 0.68, 1.41) | 0.98 | (0.65, 1.47) | 0.00 | (-0.04, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1989 |
| Low, moderate or high | 2430 | 87 | 3.6 | 2495 | 62 | 2.5 | 0.0245 | 0.69 | ( 0.50, 0.96) | 0.69 | (0.49, 0.95) | -0.01 | (-0.02, 0.00) | |
| Very high | 834 | 87 | 10.4 | 820 | 78 | 9.5 | 0.5744 | 0.92 | ( 0.69, 1.23) | 0.91 | (0.66, 1.26) | -0.01 | (-0.04, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2419 |
| No | 572 | 46 | 8.0 | 578 | 29 | 5.0 | 0.0387 | 0.62 | ( 0.40, 0.98) | 0.61 | (0.37, 0.98) | -0.03 | (-0.06, 0.00) | |
| Yes | 2703 | 128 | 4.7 | 2752 | 111 | 4.0 | 0.1985 | 0.85 | ( 0.66, 1.09) | 0.84 | (0.65, 1.09) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4929 |
| No | 344 | 22 | 6.4 | 349 | 14 | 4.0 | 0.1681 | 0.64 | ( 0.34, 1.21) | 0.63 | (0.32, 1.23) | -0.02 | (-0.06, 0.01) | |
| Yes | 2931 | 152 | 5.2 | 2981 | 126 | 4.2 | 0.0776 | 0.81 | ( 0.65, 1.02) | 0.80 | (0.63, 1.02) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.8003 |
| No | 275 | 7 | 2.5 | 307 | 7 | 2.3 | 0.8384 | 0.90 | ( 0.33, 2.46) | 0.90 | (0.32, 2.51) | 0.00 | (-0.03, 0.02) | |
| Yes | 3000 | 167 | 5.6 | 3023 | 133 | 4.4 | 0.0358 | 0.79 | ( 0.63, 0.98) | 0.78 | (0.62, 0.98) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 164 | 5.0 | 3330 | 165 | 5.0 | 0.9156 | 0.99 ( 0.80, 1.22) | 0.99 (0.79, 1.23) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 115 | 3.5 | 3330 | 129 | 3.9 | 0.4442 | 1.10 | ( 0.86, 1.41) | 1.11 (0.86, 1.43) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 108 | 3.3 | 3330 | 90 | 2.7 | 0.1508 | 0.82 | ( 0.62, 1.08) | 0.81 | (0.61, 1.08) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 96 | 2.9 | 3330 | 95 | 2.9 | 0.8384 | 0.97 ( 0.73, 1.28) | 0.97 (0.73, 1.29) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 63 | 1.9 | 3330 | 92 | 2.8 | 0.0250 | 1.43 | ( 1.04, 1.97) | 1.45 | (1.05, 2.00) | 0.01 | ( 0.00, 0.02) | |
| Study | | | | | | | | | | | | | | 0.1827 |
| 1245.110 | 2001 | 40 | 2.0 | 2052 | 68 | 3.3 | 0.0094 | 1.66 | ( 1.13, 2.44) | 1.68 | (1.13, 2.50) | 0.01 | ( 0.00, 0.02) | |
| 1245.121 | 1274 | 23 | 1.8 | 1278 | 24 | 1.9 | 0.8915 | 1.04 | ( 0.59, 1.83) | 1.04 | (0.58, 1.85) | 0.00 | (-0.01, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.1870 |
| Male | 2023 | 44 | 2.2 | 2068 | 55 | 2.7 | 0.3150 | 1.22 | ( 0.83, 1.81) | 1.23 | (0.82, 1.83) | 0.00 | ( 0.00, 0.01) | |
| Female | 1252 | 19 | 1.5 | 1262 | 37 | 2.9 | 0.0172 | 1.92 | ( 1.11, 3.33) | 1.95 | (1.12, 3.41) | 0.01 | ( 0.00, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.3813 |
| <65 | 766 | 10 | 1.3 | 705 | 9 | 1.3 | 0.9579 | 0.98 | ( 0.40, 2.39) | 0.98 | (0.39, 2.42) | 0.00 | (-0.01, 0.01) | |
| >=65 | 2509 | 53 | 2.1 | 2625 | 83 | 3.2 | 0.0190 | 1.50 | ( 1.07, 2.10) | 1.51 | (1.07, 2.15) | 0.01 | ( 0.00, 0.02) | |
| Region | | | | | | | | | | | | | | 0.4933 |
| North America | 434 | 20 | 4.6 | 432 | 22 | 5.1 | 0.7422 | 1.10 | ( 0.61, 1.99) | 1.11 | (0.60, 2.06) | 0.00 | (-0.02, 0.03) | |
| Latin America | 931 | 7 | 0.8 | 944 | 17 | 1.8 | 0.0415 | 2.42 | ( 1.01, 5.80) | 2.44 | (1.01, 5.92) | 0.01 | ( 0.00, 0.02) | |
| Europe | 1334 | 24 | 1.8 | 1361 | 31 | 2.3 | 0.3757 | 1.27 | ( 0.75, 2.15) | 1.28 | (0.74, 2.19) | 0.00 | (-0.01, 0.02) | |
| Asia | 405 | 6 | 1.5 | 413 | 7 | 1.7 | 0.8393 | 1.12 | ( 0.38, 3.32) | 1.12 | (0.37, 3.38) | 0.00 | (-0.02, 0.02) | |
| Other | 171 | 6 | 3.5 | 180 | 15 | 8.3 | 0.0726 | 2.20 | ( 0.91, 5.34) | 2.33 | (0.91, 6.00) | 0.05 | ( 0.00, 0.10) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7472 |
| Diabetic | 1739 | 31 | 1.8 | 1779 | 48 | 2.7 | 0.0688 | 1.51 | ( 0.97, 2.36) | 1.52 | (0.97, 2.41) | 0.01 | ( 0.00, 0.02) | |
| Non-Diabetic | 1536 | 32 | 2.1 | 1551 | 44 | 2.8 | 0.1781 | 1.36 | ( 0.87, 2.13) | 1.37 | (0.86, 2.17) | 0.01 | ( 0.00, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8035 |
| <30 | 1975 | 37 | 1.9 | 1930 | 54 | 2.8 | 0.0575 | 1.49 | ( 0.98, 2.25) | 1.50 | (0.98, 2.30) | 0.01 | ( 0.00, 0.02) | |
| >=30 | 1300 | 26 | 2.0 | 1400 | 38 | 2.7 | 0.2041 | 1.37 | ( 0.84, 2.24) | 1.38 | (0.84, 2.29) | 0.01 | ( 0.00, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7552 |
| <130 | 1684 | 33 | 2.0 | 1687 | 50 | 3.0 | 0.0650 | 1.50 | ( 0.97, 2.32) | 1.52 | (0.97, 2.37) | 0.01 | ( 0.00, 0.02) | |
| >=130 | 1591 | 30 | 1.9 | 1643 | 42 | 2.6 | 0.1945 | 1.36 | ( 0.85, 2.16) | 1.37 | (0.85, 2.19) | 0.01 | ( 0.00, 0.02) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio | Risk (95% CI) | Odds ratio | Odds (95% CI) | Risk diff. | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3148 |
| <75 | 1653 | 43 | 2.6 | 1612 | 50 | 3.1 | 0.4077 | 1.19 | ( 0.79, 1.77) | 1.19 | (0.79, 1.80) | 0.00 | (-0.01, 0.02) | |
| 75 to <85 | 1005 | 14 | 1.4 | 1085 | 29 | 2.7 | 0.0387 | 1.92 | ( 1.02, 3.62) | 1.95 | (1.02, 3.71) | 0.01 | ( 0.00, 0.02) | |
| >=85 | 617 | 6 | 1.0 | 633 | 13 | 2.1 | 0.1190 | 2.11 | ( 0.81, 5.52) | 2.13 | (0.81, 5.65) | 0.01 | ( 0.00, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0980 |
| <30 | 250 | 4 | 1.6 | 263 | 17 | 6.5 | 0.0052 | 4.00 | ( 1.39,11.54) | 4.20 | (1.40,12.58) | 0.05 | ( 0.02, 0.08) | |
| 30 to <45 | 898 | 22 | 2.4 | 909 | 24 | 2.6 | 0.8120 | 1.07 | ( 0.61, 1.90) | 1.07 | (0.60, 1.93) | 0.00 | (-0.01, 0.02) | |
| >=45 | 2126 | 37 | 1.7 | 2158 | 51 | 2.4 | 0.1554 | 1.35 | ( 0.89, 2.06) | 1.36 | (0.89, 2.09) | 0.01 | ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.5911 |
| Normal (<30) | 1216 | 24 | 2.0 | 1243 | 31 | 2.5 | 0.3857 | 1.26 | ( 0.74, 2.14) | 1.27 | (0.74, 2.18) | 0.01 | (-0.01, 0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 29 | 1.9 | 1546 | 50 | 3.2 | 0.0176 | 1.72 | ( 1.09, 2.70) | 1.74 | (1.10, 2.77) | 0.01 | ( 0.00, 0.02) | |
| Macroalbuminuria (>300) | 500 | 9 | 1.8 | 525 | 11 | 2.1 | 0.7345 | 1.16 | ( 0.49, 2.76) | 1.16 | (0.48, 2.82) | 0.00 | (-0.01, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2061 |
| Low, moderate or high | 2430 | 45 | 1.9 | 2495 | 59 | 2.4 | 0.2176 | 1.27 | ( 0.87, 1.87) | 1.28 | (0.86, 1.89) | 0.01 | ( 0.00, 0.01) | |
| Very high | 834 | 17 | 2.0 | 820 | 33 | 4.0 | 0.0169 | 1.99 | ( 1.12, 3.54) | 2.03 | (1.12, 3.68) | 0.02 | ( 0.00, 0.04) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.2497 |
| No | 572 | 16 | 2.8 | 578 | 31 | 5.4 | 0.0277 | 1.92 | ( 1.06, 3.47) | 1.97 | (1.07, 3.65) | 0.03 | ( 0.00, 0.05) | |
| Yes | 2703 | 47 | 1.7 | 2752 | 61 | 2.2 | 0.2108 | 1.27 | ( 0.87, 1.85) | 1.28 | (0.87, 1.88) | 0.00 | ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4948 |
| No | 344 | 10 | 2.9 | 349 | 11 | 3.2 | 0.8356 | 1.09 | ( 0.47, 2.53) | 1.10 | (0.46, 2.61) | 0.00 | (-0.02, 0.03) | |
| Yes | 2931 | 53 | 1.8 | 2981 | 81 | 2.7 | 0.0198 | 1.50 | ( 1.06, 2.11) | 1.51 | (1.07, 2.15) | 0.01 | ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline use of diuretics | | | | | | | | | | | 0.3643 |
| No | 275 | 2 | 0.7 | 307 | 7 | 2.3 | 0.1510 | 2.70 ( 0.66,11.15) | 2.75 (0.65,11.56) | 0.02 (-0.01, 0.04) | |
| Yes | 3000 | 61 | 2.0 | 3023 | 85 | 2.8 | 0.0508 | 1.38 (<1.00, 1.91) | 1.39 (1.00, 1.94) | 0.01 ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 90 | 2.7 | 3330 | 79 | 2.4 | 0.3340 | 0.86 ( 0.64, 1.16) | 0.86 (0.63, 1.17) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Neoplasms benign, malignant and unspecified (incl cysts and polyps)

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 78 | 2.4 | 3330 | 82 | 2.5 | 0.8479 | 1.03 | ( 0.76, 1.40) | 1.03 (0.75, 1.41) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 71 | 2.2 | 3330 | 79 | 2.4 | 0.5851 | 1.09 ( 0.80, 1.50) | 1.09 (0.79, 1.51) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 41 | 1.3 | 3330 | 27 | 0.8 | 0.0758 | 0.65 ( 0.40, 1.05) | 0.64 (0.40, 1.05) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 39 | 1.2 | 3330 | 26 | 0.8 | 0.0866 | 0.65 ( 0.40, 1.07) | 0.65 (0.39, 1.07) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.4: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on SOC level by SOC occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders

| Subgroup Category | Placebo N | Placebo n | Placebo % | Empa 10mg N | Empa 10mg n | Empa 10mg % | Empa 10mg vs Placebo p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 3275 | 31 | 0.9 | 3330 | 35 | 1.1 | 0.6798 | 1.11 ( 0.68, 1.79) | 1.11 (0.68, 1.80) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

**R.5.2.5**

R.5.2.5 Adverse events on PT level

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 891 | 27.2 | 3330 | 721 | 21.7 | <0.0001 | 0.80 ( 0.73, | 0.87) | 0.74 ( 0.66, | 0.83) | -0.06 (-0.08,-0.03) | |
| Study | | | | | | | | | | | | | 0.8249 |
| 1245.110 | 2001 | 516 | 25.8 | 2052 | 418 | 20.4 | <0.0001 | 0.79 ( 0.71, | 0.88) | 0.74 ( 0.64, | 0.85) | -0.05 (-0.08,-0.03) | |
| 1245.121 | 1274 | 375 | 29.4 | 1278 | 303 | 23.7 | 0.0011 | 0.81 ( 0.71, | 0.92) | 0.75 ( 0.62, | 0.89) | -0.06 (-0.09,-0.02) | |
| Sex | | | | | | | | | | | | | 0.6651 |
| Male | 2023 | 571 | 28.2 | 2068 | 458 | 22.1 | <0.0001 | 0.78 ( 0.71, | 0.87) | 0.72 ( 0.63, | 0.83) | -0.06 (-0.09,-0.03) | |
| Female | 1252 | 320 | 25.6 | 1262 | 263 | 20.8 | 0.0054 | 0.82 ( 0.71, | 0.94) | 0.77 ( 0.64, | 0.93) | -0.05 (-0.08,-0.01) | |
| Age [years] | | | | | | | | | | | | | 0.2024 |
| <65 | 766 | 209 | 27.3 | 705 | 169 | 24.0 | 0.1550 | 0.88 ( 0.74, | 1.05) | 0.84 ( 0.67, | 1.07) | -0.03 (-0.08, 0.01) | |
| >=65 | 2509 | 682 | 27.2 | 2625 | 552 | 21.0 | <0.0001 | 0.77 ( 0.70, | 0.85) | 0.71 ( 0.63, | 0.81) | -0.06 (-0.08,-0.04) | |
| Region | | | | | | | | | | | | | 0.6013 |
| North America | 434 | 86 | 19.8 | 432 | 76 | 17.6 | 0.4019 | 0.89 ( 0.67, | 1.17) | 0.86 ( 0.61, | 1.22) | -0.02 (-0.07, 0.03) | |
| Latin America | 931 | 263 | 28.2 | 944 | 220 | 23.3 | 0.0136 | 0.82 ( 0.71, | 0.96) | 0.77 ( 0.63, | 0.95) | -0.05 (-0.09,-0.01) | |
| Europe | 1334 | 380 | 28.5 | 1361 | 303 | 22.3 | 0.0002 | 0.78 ( 0.69, | 0.89) | 0.72 ( 0.60, | 0.86) | -0.06 (-0.09,-0.03) | |
| Asia | 405 | 122 | 30.1 | 413 | 84 | 20.3 | 0.0016 | 0.68 ( 0.54, | 0.87) | 0.60 ( 0.43, | 0.82) | -0.10 (-0.15,-0.04) | |
| Other | 171 | 40 | 23.4 | 180 | 38 | 21.1 | 0.5610 | 0.89 ( 0.60, | 1.31) | 0.86 ( 0.52, | 1.43) | -0.03 (-0.11, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.7804 |
| Diabetic | 1739 | 496 | 28.5 | 1779 | 408 | 22.9 | 0.0002 | 0.80 ( 0.72, | 0.90) | 0.75 ( 0.64, | 0.87) | -0.06 (-0.08,-0.03) | |
| Non-Diabetic | 1536 | 395 | 25.7 | 1551 | 313 | 20.2 | 0.0003 | 0.79 ( 0.69, | 0.89) | 0.73 ( 0.62, | 0.86) | -0.06 (-0.08,-0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.2809 |
| <30 | 1975 | 547 | 27.7 | 1930 | 408 | 21.1 | <0.0001 | 0.76 ( 0.68, | 0.86) | 0.70 ( 0.61, | 0.81) | -0.07 (-0.09,-0.04) | |
| >=30 | 1300 | 344 | 26.5 | 1400 | 313 | 22.4 | 0.0109 | 0.84 ( 0.74, | 0.96) | 0.80 ( 0.67, | 0.95) | -0.04 (-0.07,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.9619 |
| <130 | 1684 | 492 | 29.2 | 1687 | 393 | 23.3 | 0.0001 | 0.80 ( 0.71, | 0.90) | 0.74 ( 0.63, | 0.86) | -0.06 (-0.09,-0.03) | |
| >=130 | 1591 | 399 | 25.1 | 1643 | 328 | 20.0 | 0.0005 | 0.80 ( 0.70, | 0.90) | 0.74 ( 0.63, | 0.88) | -0.05 (-0.08,-0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.0796 |
| <75 | 1653 | 456 | 27.6 | 1612 | 389 | 24.1 | 0.0258 | 0.88 ( 0.78, 0.98) | 0.84 ( 0.71, 0.98) | -0.03 (-0.06, 0.00) | |
| 75 to <85 | 1005 | 271 | 27.0 | 1085 | 211 | 19.4 | <0.0001 | 0.72 ( 0.62, 0.84) | 0.65 ( 0.53, 0.80) | -0.08 (-0.11,-0.04) | |
| >=85 | 617 | 164 | 26.6 | 633 | 121 | 19.1 | 0.0016 | 0.72 ( 0.58, 0.88) | 0.65 ( 0.50, 0.85) | -0.07 (-0.12,-0.03) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.1480 |
| <30 | 250 | 84 | 33.6 | 263 | 85 | 32.3 | 0.6759 | 0.95 ( 0.74, 1.21) | 0.92 ( 0.64, 1.34) | -0.02 (-0.10, 0.06) | |
| 30 to <45 | 898 | 254 | 28.3 | 909 | 218 | 24.0 | 0.0379 | 0.85 ( 0.73, 0.99) | 0.80 ( 0.65, 0.99) | -0.04 (-0.08, 0.00) | |
| >=45 | 2126 | 553 | 26.0 | 2158 | 418 | 19.4 | <0.0001 | 0.75 ( 0.67, 0.84) | 0.69 ( 0.59, 0.79) | -0.07 (-0.09,-0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.6545 |
| Normal (<30) | 1216 | 289 | 23.8 | 1243 | 225 | 18.1 | 0.0006 | 0.76 ( 0.65, 0.89) | 0.71 ( 0.58, 0.86) | -0.06 (-0.09,-0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 431 | 27.8 | 1546 | 358 | 23.2 | 0.0030 | 0.83 ( 0.74, 0.94) | 0.78 ( 0.67, 0.92) | -0.05 (-0.08,-0.02) | |
| Macroalbuminuria (>300) | 500 | 167 | 33.4 | 525 | 138 | 26.3 | 0.0115 | 0.78 ( 0.65, 0.95) | 0.71 ( 0.54, 0.93) | -0.07 (-0.13,-0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.1835 |
| Low, moderate or high | 2430 | 615 | 25.3 | 2495 | 487 | 19.5 | <0.0001 | 0.77 ( 0.70, 0.86) | 0.72 ( 0.63, 0.82) | -0.06 (-0.08,-0.03) | |
| Very high | 834 | 272 | 32.6 | 820 | 234 | 28.5 | 0.0663 | 0.87 ( 0.75, 1.01) | 0.82 ( 0.67, 1.01) | -0.04 (-0.09, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.0257 |
| No | 572 | 155 | 27.1 | 578 | 152 | 26.3 | 0.7590 | 0.97 ( 0.80, 1.18) | 0.96 ( 0.74, 1.25) | -0.01 (-0.06, 0.04) | |
| Yes | 2703 | 736 | 27.2 | 2752 | 569 | 20.7 | <0.0001 | 0.76 ( 0.69, 0.84) | 0.70 ( 0.62, 0.79) | -0.07 (-0.09,-0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.1511 |
| No | 344 | 89 | 25.9 | 349 | 86 | 24.6 | 0.7033 | 0.95 ( 0.74, 1.23) | 0.94 ( 0.66, 1.32) | -0.01 (-0.08, 0.05) | |
| Yes | 2931 | 802 | 27.4 | 2981 | 635 | 21.3 | <0.0001 | 0.78 ( 0.71, 0.85) | 0.72 ( 0.64, 0.81) | -0.06 (-0.08,-0.04) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | 0.2716 |
| No | 275 | 49 | 17.8 | 307 | 35 | 11.4 | 0.0290 | 0.64 | ( 0.43, 0.96) | 0.60 | ( 0.37, 0.95) | -0.06 (-0.12,-0.01) | |
| Yes | 3000 | 842 | 28.1 | 3023 | 686 | 22.7 | <0.0001 | 0.81 | ( 0.74, 0.88) | 0.75 | ( 0.67, 0.85) | -0.05 (-0.08,-0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 254 | 7.8 | 3330 | 226 | 6.8 | 0.1223 | 0.87 ( 0.73, 1.04) | 0.86 ( 0.72, 1.04) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 118 | 3.6 | 3330 | 83 | 2.5 | 0.0085 | 0.69 | ( 0.52, 0.91) | 0.68 | ( 0.51, 0.91) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.2914 |
| 1245.110 | 2001 | 72 | 3.6 | 2052 | 57 | 2.8 | 0.1369 | 0.77 | ( 0.55, 1.09) | 0.77 | ( 0.54, 1.09) | -0.01 | (-0.02, 0.00) | |
| 1245.121 | 1274 | 46 | 3.6 | 1278 | 26 | 2.0 | 0.0162 | 0.56 | ( 0.35, 0.91) | 0.55 | ( 0.34, 0.90) | -0.02 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4085 |
| Male | 2023 | 76 | 3.8 | 2068 | 49 | 2.4 | 0.0099 | 0.63 | ( 0.44, 0.90) | 0.62 | ( 0.43, 0.89) | -0.01 | (-0.02, 0.00) | |
| Female | 1252 | 42 | 3.4 | 1262 | 34 | 2.7 | 0.3284 | 0.80 | ( 0.51, 1.25) | 0.80 | ( 0.50, 1.26) | -0.01 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.9792 |
| <65 | 766 | 25 | 3.3 | 705 | 16 | 2.3 | 0.2474 | 0.70 | ( 0.37, 1.29) | 0.69 | ( 0.36, 1.30) | -0.01 | (-0.03, 0.01) | |
| >=65 | 2509 | 93 | 3.7 | 2625 | 67 | 2.6 | 0.0175 | 0.69 | ( 0.51, 0.94) | 0.68 | ( 0.49, 0.94) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | 0.0921 |
| North America | 434 | 80 | 18.4 | 432 | 64 | 14.8 | 0.1510 | 0.80 | ( 0.59, 1.08) | 0.77 | ( 0.54, 1.10) | -0.04 | (-0.09, 0.01) | |
| Latin America | 931 | 16 | 1.7 | 944 | 5 | 0.5 | 0.0138 | 0.31 | ( 0.11, 0.83) | 0.30 | ( 0.11, 0.83) | -0.01 | (-0.02, 0.00) | |
| Europe | 1334 | 8 | 0.6 | 1361 | 10 | 0.7 | 0.6516 | 1.24 | ( 0.49, 3.12) | 1.24 | ( 0.49, 3.15) | 0.00 | ( 0.00, 0.01) | |
| Asia | 405 | 6 | 1.5 | 413 | 4 | 1.0 | 0.5279 | 0.68 | ( 0.20, 2.29) | 0.68 | ( 0.20, 2.28) | -0.01 | (-0.02, 0.01) | |
| Other | 171 | 8 | 4.7 | 180 | 0 | 0 | 0.0077 | 0.11 | ( 0.01, 0.81) | 0.10 | ( 0.01, 0.80) | -0.05 | (-0.08,-0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8739 |
| Diabetic | 1739 | 72 | 4.1 | 1779 | 50 | 2.8 | 0.0308 | 0.68 | ( 0.48, 0.97) | 0.67 | ( 0.46, 0.97) | -0.01 | (-0.03, 0.00) | |
| Non-Diabetic | 1536 | 46 | 3.0 | 1551 | 33 | 2.1 | 0.1266 | 0.71 | ( 0.46, 1.10) | 0.70 | ( 0.45, 1.11) | -0.01 | (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.6489 |
| <30 | 1975 | 62 | 3.1 | 1930 | 39 | 2.0 | 0.0271 | 0.64 | ( 0.43, 0.95) | 0.63 | ( 0.42, 0.95) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1300 | 56 | 4.3 | 1400 | 44 | 3.1 | 0.1100 | 0.73 | ( 0.50, 1.08) | 0.72 | ( 0.48, 1.08) | -0.01 | (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5590 |
| <130 | 1684 | 67 | 4.0 | 1687 | 50 | 3.0 | 0.1066 | 0.74 | ( 0.52, 1.07) | 0.74 | ( 0.51, 1.07) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1591 | 51 | 3.2 | 1643 | 33 | 2.0 | 0.0337 | 0.63 | ( 0.41, 0.97) | 0.62 | ( 0.40, 0.97) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.1550 |
| <75 | 1653 | 59 | 3.6 | 1612 | 50 | 3.1 | 0.4463 | 0.87 ( 0.60, | 1.25) | 0.86 ( 0.59, | 1.26) | 0.00 (-0.02, 0.01) | |
| 75 to <85 | 1005 | 31 | 3.1 | 1085 | 21 | 1.9 | 0.0925 | 0.63 ( 0.36, | 1.09) | 0.62 ( 0.35, | 1.09) | -0.01 (-0.02, 0.00) | |
| >=85 | 617 | 28 | 4.5 | 633 | 12 | 1.9 | 0.0079 | 0.42 ( 0.21, | 0.81) | 0.41 ( 0.20, | 0.81) | -0.03 (-0.05,-0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.5425 |
| <30 | 250 | 17 | 6.8 | 263 | 13 | 4.9 | 0.5165 | 0.80 ( 0.40, | 1.58) | 0.78 ( 0.37, | 1.65) | -0.01 (-0.05, 0.03) | |
| 30 to <45 | 898 | 30 | 3.3 | 909 | 26 | 2.9 | 0.5536 | 0.86 ( 0.51, | 1.43) | 0.85 ( 0.50, | 1.45) | 0.00 (-0.02, 0.01) | |
| >=45 | 2126 | 71 | 3.3 | 2158 | 44 | 2.0 | 0.0087 | 0.61 ( 0.42, | 0.89) | 0.60 ( 0.41, | 0.88) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.2761 |
| Normal (<30) | 1216 | 30 | 2.5 | 1243 | 21 | 1.7 | 0.1738 | 0.68 ( 0.39, | 1.19) | 0.68 ( 0.39, | 1.19) | -0.01 (-0.02, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 60 | 3.9 | 1546 | 49 | 3.2 | 0.2893 | 0.82 ( 0.56, | 1.19) | 0.81 ( 0.55, | 1.19) | -0.01 (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 500 | 28 | 5.6 | 525 | 13 | 2.5 | 0.0114 | 0.44 ( 0.23, | 0.85) | 0.43 ( 0.22, | 0.84) | -0.03 (-0.06,-0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.2035 |
| Low, moderate or high | 2430 | 77 | 3.2 | 2495 | 48 | 1.9 | 0.0057 | 0.61 ( 0.43, | 0.87) | 0.60 ( 0.42, | 0.86) | -0.01 (-0.02, 0.00) | |
| Very high | 834 | 41 | 4.9 | 820 | 35 | 4.3 | 0.5606 | 0.88 ( 0.57, | 1.36) | 0.87 ( 0.55, | 1.38) | -0.01 (-0.03, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.3783 |
| No | 572 | 32 | 5.6 | 578 | 27 | 4.7 | 0.4836 | 0.84 ( 0.51, | 1.38) | 0.83 ( 0.49, | 1.40) | -0.01 (-0.03, 0.02) | |
| Yes | 2703 | 86 | 3.2 | 2752 | 56 | 2.0 | 0.0078 | 0.64 ( 0.46, | 0.89) | 0.63 ( 0.45, | 0.89) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.9305 |
| No | 344 | 15 | 4.4 | 349 | 11 | 3.2 | 0.3748 | 0.71 ( 0.33, | 1.52) | 0.70 ( 0.32, | 1.54) | -0.01 (-0.04, 0.02) | |
| Yes | 2931 | 103 | 3.5 | 2981 | 72 | 2.4 | 0.0123 | 0.69 ( 0.51, | 0.92) | 0.68 ( 0.50, | 0.92) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.7075 |
| No | 275 | 5 | 1.8 | 307 | 3 | 1.0 | 0.3777 | 0.53 ( 0.13, 2.21) | 0.53 ( 0.12, 2.23) | -0.01 (-0.03, 0.01) | |
| Yes | 3000 | 113 | 3.8 | 3023 | 80 | 2.6 | 0.0133 | 0.70 ( 0.53, 0.93) | 0.69 ( 0.52, 0.93) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina pectoris

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 74 | 2.3 | 3330 | 71 | 2.1 | 0.7141 | 0.94 ( 0.68, 1.30) | 0.94 ( 0.68, 1.31) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 63 | 1.9 | 3330 | 65 | 2.0 | 0.9479 | 1.01 ( 0.72, 1.43) | 1.01 ( 0.71, 1.44) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 61 | 1.9 | 3330 | 63 | 1.9 | 0.9012 | 1.02 | ( 0.72, 1.45) | 1.02 | ( 0.72, 1.46) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 59 | 1.8 | 3330 | 39 | 1.2 | 0.0350 | 0.65 | ( 0.44, 0.97) | 0.65 | ( 0.43, 0.97) | -0.01 | (-0.01, 0.00) | |
| Study | | | | | | | | | | | | | | 0.5533 |
| 1245.110 | 2001 | 32 | 1.6 | 2052 | 19 | 0.9 | 0.0546 | 0.58 | ( 0.33, 1.02) | 0.58 | ( 0.32, 1.02) | -0.01 | (-0.01, 0.00) | |
| 1245.121 | 1274 | 27 | 2.1 | 1278 | 20 | 1.6 | 0.2978 | 0.74 | ( 0.42, 1.31) | 0.73 | ( 0.41, 1.32) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4716 |
| Male | 2023 | 38 | 1.9 | 2068 | 28 | 1.4 | 0.1840 | 0.72 | ( 0.44, 1.17) | 0.72 | ( 0.44, 1.17) | -0.01 | (-0.01, 0.00) | |
| Female | 1252 | 21 | 1.7 | 1262 | 11 | 0.9 | 0.0745 | 0.52 | ( 0.25, 1.08) | 0.52 | ( 0.25, 1.08) | -0.01 | (-0.02, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.3305 |
| <65 | 766 | 16 | 2.1 | 705 | 13 | 1.8 | 0.7550 | 0.89 | ( 0.43, 1.84) | 0.89 | ( 0.42, 1.86) | 0.00 | (-0.02, 0.01) | |
| >=65 | 2509 | 43 | 1.7 | 2625 | 26 | 1.0 | 0.0244 | 0.58 | ( 0.36, 0.94) | 0.57 | ( 0.35, 0.94) | -0.01 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.5098 |
| North America | 434 | 32 | 7.4 | 432 | 27 | 6.3 | 0.5143 | 0.85 | ( 0.52, 1.39) | 0.84 | ( 0.49, 1.42) | -0.01 | (-0.04, 0.02) | |
| Latin America | 931 | 4 | 0.4 | 944 | 2 | 0.2 | 0.4327 | 0.54 | ( 0.11, 2.56) | 0.54 | ( 0.11, 2.56) | 0.00 | (-0.01, 0.00) | |
| Europe | 1334 | 16 | 1.2 | 1361 | 5 | 0.4 | 0.0149 | 0.31 | ( 0.11, 0.84) | 0.31 | ( 0.11, 0.84) | -0.01 | (-0.01, 0.00) | |
| Asia | 405 | 7 | 1.7 | 413 | 5 | 1.2 | 0.5267 | 0.70 | ( 0.23, 2.15) | 0.69 | ( 0.22, 2.18) | -0.01 | (-0.02, 0.01) | |
| Other | 171 | 0 | 0 | 180 | 0 | 0 | 0.9906 | 0.98 | ( 0.06, 15.54) | 0.98 | ( 0.06, 15.88) | 0.00 | (-0.02, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.2161 |
| Diabetic | 1739 | 40 | 2.3 | 1779 | 31 | 1.7 | 0.2430 | 0.76 | ( 0.48, 1.21) | 0.75 | ( 0.47, 1.21) | -0.01 | (-0.01, 0.00) | |
| Non-Diabetic | 1536 | 19 | 1.2 | 1551 | 8 | 0.5 | 0.0319 | 0.42 | ( 0.18, 0.95) | 0.42 | ( 0.18, 0.95) | -0.01 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.4474 |
| <30 | 1975 | 32 | 1.6 | 1930 | 17 | 0.9 | 0.0409 | 0.55 | ( 0.31, 0.98) | 0.55 | ( 0.30, 0.98) | -0.01 | (-0.01, 0.00) | |
| >=30 | 1300 | 27 | 2.1 | 1400 | 22 | 1.6 | 0.3125 | 0.75 | ( 0.43, 1.31) | 0.75 | ( 0.42, 1.32) | -0.01 | (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.9138 |
| <130 | 1684 | 33 | 2.0 | 1687 | 21 | 1.2 | 0.1040 | 0.64 | ( 0.37, 1.10) | 0.64 | ( 0.37, 1.10) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1591 | 26 | 1.6 | 1643 | 18 | 1.1 | 0.1850 | 0.67 | ( 0.37, 1.22) | 0.67 | ( 0.36, 1.22) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.2142 |
| <75 | 1653 | 39 | 2.4 | 1612 | 22 | 1.4 | 0.0372 | 0.58 | ( 0.35, | 0.97) | 0.57 ( 0.34, | 0.97) | -0.01 (-0.02, 0.00) | |
| 75 to <85 | 1005 | 10 | 1.0 | 1085 | 13 | 1.2 | 0.6623 | 1.20 | ( 0.53, | 2.73) | 1.20 ( 0.52, | 2.76) | 0.00 (-0.01, 0.01) | |
| >=85 | 617 | 10 | 1.6 | 633 | 4 | 0.6 | 0.0959 | 0.39 | ( 0.12, | 1.23) | 0.38 ( 0.12, | 1.23) | -0.01 (-0.02, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.5235 |
| <30 | 250 | 12 | 4.8 | 263 | 5 | 1.9 | 0.0588 | 0.37 | ( 0.13, | 1.09) | 0.36 ( 0.12, | 1.06) | -0.03 (-0.06, 0.00) | |
| 30 to <45 | 898 | 14 | 1.6 | 909 | 11 | 1.2 | 0.5288 | 0.78 | ( 0.35, | 1.70) | 0.77 ( 0.35, | 1.72) | 0.00 (-0.01, 0.01) | |
| >=45 | 2126 | 33 | 1.6 | 2158 | 23 | 1.1 | 0.1690 | 0.69 | ( 0.41, | 1.17) | 0.69 ( 0.40, | 1.18) | 0.00 (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.9526 |
| Normal (<30) | 1216 | 11 | 0.9 | 1243 | 8 | 0.6 | 0.4669 | 0.72 | ( 0.29, | 1.77) | 0.71 ( 0.29, | 1.78) | 0.00 (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 32 | 2.1 | 1546 | 21 | 1.4 | 0.1312 | 0.66 | ( 0.38, | 1.14) | 0.65 ( 0.38, | 1.14) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 500 | 16 | 3.2 | 525 | 10 | 1.9 | 0.1856 | 0.59 | ( 0.27, | 1.30) | 0.59 ( 0.26, | 1.30) | -0.01 (-0.03, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.5207 |
| Low, moderate or high | 2430 | 32 | 1.3 | 2495 | 24 | 1.0 | 0.2522 | 0.74 | ( 0.43, | 1.25) | 0.73 ( 0.43, | 1.25) | 0.00 (-0.01, 0.00) | |
| Very high | 834 | 27 | 3.2 | 820 | 15 | 1.8 | 0.0682 | 0.56 | ( 0.30, | 1.05) | 0.56 ( 0.29, | 1.05) | -0.01 (-0.03, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5353 |
| No | 572 | 12 | 2.1 | 578 | 10 | 1.7 | 0.6432 | 0.82 | ( 0.36, | 1.89) | 0.82 ( 0.35, | 1.91) | 0.00 (-0.02, 0.01) | |
| Yes | 2703 | 47 | 1.7 | 2752 | 29 | 1.1 | 0.0322 | 0.61 | ( 0.38, | 0.96) | 0.60 ( 0.38, | 0.96) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.3148 |
| No | 344 | 7 | 2.0 | 349 | 2 | 0.6 | 0.1063 | 0.33 | ( 0.08, | 1.36) | 0.32 ( 0.08, | 1.36) | -0.01 (-0.03, 0.00) | |
| Yes | 2931 | 52 | 1.8 | 2981 | 37 | 1.2 | 0.0961 | 0.70 | ( 0.46, | 1.07) | 0.70 ( 0.46, | 1.07) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.6325 |
| No | 275 | 4 | 1.5 | 307 | 2 | 0.7 | 0.3264 | 0.44 ( 0.08, 2.39) | 0.43 ( 0.08, 2.40) | -0.01 (-0.02, 0.01) | |
| Yes | 3000 | 55 | 1.8 | 3023 | 37 | 1.2 | 0.0550 | 0.67 ( 0.44, 1.01) | 0.66 ( 0.44, 1.01) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure chronic

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 58 | 1.8 | 3330 | 58 | 1.7 | 0.9272 | 0.98 ( 0.69, 1.41) | 0.98 ( 0.68, 1.42) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 31 | 0.9 | 3330 | 47 | 1.4 | 0.0817 | 1.49 ( 0.95, 2.34) | 1.50 ( 0.95, 2.36) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial flutter

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 44 | 1.3 | 3330 | 45 | 1.4 | 0.9755 | 1.01 ( 0.67, 1.52) | 1.01 ( 0.66, 1.53) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Coronary artery disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 3275 | 39 | 1.2 | 3330 | 23 | 0.7 | 0.0338 | 0.58 ( 0.35, | 0.97) | 0.57 ( 0.34, | 0.96) | -0.01 (-0.01, | 0.00) | |
| Study | | | | | | | | | | | | | | 0.1866 |
| 1245.110 | 2001 | 28 | 1.4 | 2052 | 20 | 1.0 | 0.2116 | 0.70 ( 0.39, | 1.23) | 0.69 ( 0.39, | 1.24) | 0.00 (-0.01, | 0.00) | |
| 1245.121 | 1274 | 11 | 0.9 | 1278 | 3 | 0.2 | 0.0316 | 0.27 ( 0.08, | 0.97) | 0.27 ( 0.08, | 0.97) | -0.01 (-0.01, | 0.00) | |
| Sex | | | | | | | | | | | | | | 0.7085 |
| Male | 2023 | 25 | 1.2 | 2068 | 16 | 0.8 | 0.1365 | 0.63 ( 0.33, | 1.17) | 0.62 ( 0.33, | 1.17) | 0.00 (-0.01, | 0.00) | |
| Female | 1252 | 14 | 1.1 | 1262 | 7 | 0.6 | 0.1248 | 0.51 ( 0.21, | 1.23) | 0.51 ( 0.21, | 1.23) | -0.01 (-0.01, | 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.5863 |
| <65 | 766 | 7 | 0.9 | 705 | 5 | 0.7 | 0.6543 | 0.77 ( 0.24, | 2.43) | 0.77 ( 0.24, | 2.44) | 0.00 (-0.01, | 0.01) | |
| >=65 | 2509 | 32 | 1.3 | 2625 | 18 | 0.7 | 0.0321 | 0.54 ( 0.30, | 0.96) | 0.54 ( 0.30, | 0.96) | -0.01 (-0.01, | 0.00) | |
| Region | | | | | | | | | | | | | | 0.8476 |
| North America | 434 | 11 | 2.5 | 432 | 5 | 1.2 | 0.1311 | 0.46 ( 0.16, | 1.30) | 0.45 ( 0.15, | 1.30) | -0.01 (-0.03, | 0.00) | |
| Latin America | 931 | 6 | 0.6 | 944 | 3 | 0.3 | 0.3428 | 0.54 ( 0.15, | 1.97) | 0.54 ( 0.15, | 1.98) | 0.00 (-0.01, | 0.00) | |
| Europe | 1334 | 17 | 1.3 | 1361 | 14 | 1.0 | 0.5436 | 0.80 ( 0.40, | 1.63) | 0.80 ( 0.39, | 1.64) | 0.00 (-0.01, | 0.01) | |
| Asia | 405 | 3 | 0.7 | 413 | 1 | 0.2 | 0.3718 | 0.43 ( 0.06, | 2.93) | 0.42 ( 0.06, | 2.92) | 0.00 (-0.02, | 0.01) | |
| Other | 171 | 2 | 1.2 | 180 | 0 | 0 | 0.2895 | 0.32 ( 0.03, | 2.96) | 0.32 ( 0.03, | 3.02) | -0.01 (-0.03, | 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3428 |
| Diabetic | 1739 | 28 | 1.6 | 1779 | 14 | 0.8 | 0.0236 | 0.49 ( 0.26, | 0.92) | 0.48 ( 0.25, | 0.92) | -0.01 (-0.02, | 0.00) | |
| Non-Diabetic | 1536 | 11 | 0.7 | 1551 | 9 | 0.6 | 0.6418 | 0.82 ( 0.35, | 1.92) | 0.82 ( 0.34, | 1.93) | 0.00 (-0.01, | 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7931 |
| <30 | 1975 | 18 | 0.9 | 1930 | 11 | 0.6 | 0.2075 | 0.62 ( 0.29, | 1.31) | 0.62 ( 0.29, | 1.31) | 0.00 (-0.01, | 0.00) | |
| >=30 | 1300 | 21 | 1.6 | 1400 | 12 | 0.9 | 0.0813 | 0.54 ( 0.27, | 1.09) | 0.54 ( 0.26, | 1.09) | -0.01 (-0.02, | 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5843 |
| <130 | 1684 | 16 | 1.0 | 1687 | 11 | 0.7 | 0.3190 | 0.68 ( 0.31, | 1.46) | 0.68 ( 0.31, | 1.46) | 0.00 (-0.01, | 0.00) | |
| >=130 | 1591 | 23 | 1.4 | 1643 | 12 | 0.7 | 0.0511 | 0.51 ( 0.25, | 1.02) | 0.50 ( 0.25, | 1.02) | -0.01 (-0.01, | 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Coronary artery disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.2335 |
| <75 | 1653 | 17 | 1.0 | 1612 | 14 | 0.9 | 0.6112 | 0.83 ( 0.41, | 1.69) | 0.83 ( 0.41, | 1.70) | 0.00 (-0.01, 0.00) | |
| 75 to <85 | 1005 | 16 | 1.6 | 1085 | 5 | 0.5 | 0.0096 | 0.29 ( 0.11, | 0.79) | 0.29 ( 0.10, | 0.78) | -0.01 (-0.02, 0.00) | |
| >=85 | 617 | 6 | 1.0 | 633 | 4 | 0.6 | 0.5224 | 0.68 ( 0.21, | 2.24) | 0.68 ( 0.20, | 2.26) | 0.00 (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.3311 |
| <30 | 250 | 6 | 2.4 | 263 | 1 | 0.4 | 0.0743 | 0.23 ( 0.04, | 1.35) | 0.22 ( 0.04, | 1.34) | -0.02 (-0.04, 0.00) | |
| 30 to <45 | 898 | 10 | 1.1 | 909 | 4 | 0.4 | 0.1023 | 0.40 ( 0.12, | 1.25) | 0.39 ( 0.12, | 1.26) | -0.01 (-0.01, 0.00) | |
| >=45 | 2126 | 23 | 1.1 | 2158 | 18 | 0.8 | 0.3836 | 0.76 ( 0.41, | 1.41) | 0.76 ( 0.41, | 1.41) | 0.00 (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.0563 |
| Normal (<30) | 1216 | 8 | 0.7 | 1243 | 7 | 0.6 | 0.7577 | 0.85 ( 0.31, | 2.35) | 0.85 ( 0.31, | 2.36) | 0.00 (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 17 | 1.1 | 1546 | 15 | 1.0 | 0.7028 | 0.87 ( 0.44, | 1.75) | 0.87 ( 0.43, | 1.76) | 0.00 (-0.01, 0.01) | |
| Macroalbuminuria (>300) | 500 | 14 | 2.8 | 525 | 1 | 0.2 | 0.0008 | 0.10 ( 0.02, | 0.53) | 0.10 ( 0.02, | 0.52) | -0.03 (-0.04,-0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.0170 |
| Low, moderate or high | 2430 | 23 | 0.9 | 2495 | 21 | 0.8 | 0.6721 | 0.88 ( 0.49, | 1.59) | 0.88 ( 0.48, | 1.59) | 0.00 (-0.01, 0.00) | |
| Very high | 834 | 16 | 1.9 | 820 | 2 | 0.2 | 0.0011 | 0.13 ( 0.03, | 0.56) | 0.13 ( 0.03, | 0.55) | -0.02 (-0.03,-0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.3783 |
| No | 572 | 5 | 0.9 | 578 | 1 | 0.2 | 0.1282 | 0.27 ( 0.04, | 1.65) | 0.27 ( 0.04, | 1.65) | -0.01 (-0.02, 0.00) | |
| Yes | 2703 | 34 | 1.3 | 2752 | 22 | 0.8 | 0.0890 | 0.63 ( 0.37, | 1.08) | 0.63 ( 0.37, | 1.08) | 0.00 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.6417 |
| No | 344 | 7 | 2.0 | 349 | 5 | 1.4 | 0.5820 | 0.74 ( 0.25, | 2.19) | 0.73 ( 0.24, | 2.23) | -0.01 (-0.03, 0.01) | |
| Yes | 2931 | 32 | 1.1 | 2981 | 18 | 0.6 | 0.0388 | 0.55 ( 0.31, | 0.98) | 0.55 ( 0.31, | 0.98) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Coronary artery disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.4690 |
| No | 275 | 4 | 1.5 | 307 | 4 | 1.3 | 0.8784 | 0.90 ( 0.25, 3.30) | 0.90 ( 0.24, 3.37) | 0.00 (-0.02, 0.02) | |
| Yes | 3000 | 35 | 1.2 | 3023 | 19 | 0.6 | 0.0259 | 0.54 ( 0.31, 0.94) | 0.53 ( 0.30, 0.94) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Bradycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 33 | 1.0 | 3330 | 35 | 1.1 | 0.8762 | 1.04 ( 0.65, 1.67) | 1.04 ( 0.64, 1.68) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina unstable

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 23 | 0.7 | 3330 | 34 | 1.0 | 0.1632 | 1.45 ( 0.86, 2.46) | 1.46 ( 0.86, 2.48) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 276 | 8.4 | 3330 | 255 | 7.7 | 0.2449 | 0.91 ( 0.77, 1.07) | 0.90 ( 0.75, 1.07) | -0.01 (-0.02, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 227 | 6.9 | 3330 | 271 | 8.1 | 0.0670 | 1.17 ( 0.99, 1.39) | 1.19 ( 0.99, 1.43) | 0.01 ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Nasopharyngitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 156 | 4.8 | 3330 | 176 | 5.3 | 0.3297 | 1.11 ( 0.90, 1.37) | 1.12 ( 0.89, 1.39) | 0.01 (-0.01, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Upper respiratory tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 151 | 4.6 | 3330 | 131 | 3.9 | 0.1714 | 0.85 ( 0.68, 1.07) | 0.85 ( 0.67, 1.08) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Bronchitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 148 | 4.5 | 3330 | 108 | 3.2 | 0.0071 | 0.72 ( 0.56, 0.91) | | 0.71 ( 0.55, 0.91) | | -0.01 (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | 0.7476 |
| 1245.110 | 2001 | 98 | 4.9 | 2052 | 70 | 3.4 | 0.0176 | 0.70 ( 0.52, 0.94) | | 0.69 ( 0.50, 0.94) | | -0.01 (-0.03, 0.00) | |
| 1245.121 | 1274 | 50 | 3.9 | 1278 | 38 | 3.0 | 0.1880 | 0.76 ( 0.50, 1.15) | | 0.75 ( 0.49, 1.15) | | -0.01 (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | 0.1817 |
| Male | 2023 | 83 | 4.1 | 2068 | 52 | 2.5 | 0.0045 | 0.61 ( 0.44, 0.86) | | 0.60 ( 0.42, 0.86) | | -0.02 (-0.03, 0.00) | |
| Female | 1252 | 65 | 5.2 | 1262 | 56 | 4.4 | 0.3741 | 0.85 ( 0.60, 1.21) | | 0.85 ( 0.59, 1.22) | | -0.01 (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | 0.8531 |
| <65 | 766 | 26 | 3.4 | 705 | 18 | 2.6 | 0.3392 | 0.75 ( 0.41, 1.36) | | 0.74 ( 0.40, 1.37) | | -0.01 (-0.03, 0.01) | |
| >=65 | 2509 | 122 | 4.9 | 2625 | 90 | 3.4 | 0.0099 | 0.71 ( 0.54, 0.92) | | 0.69 ( 0.53, 0.92) | | -0.01 (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | 0.5885 |
| North America | 434 | 33 | 7.6 | 432 | 27 | 6.3 | 0.4327 | 0.82 ( 0.50, 1.35) | | 0.81 ( 0.48, 1.37) | | -0.01 (-0.05, 0.02) | |
| Latin America | 931 | 42 | 4.5 | 944 | 22 | 2.3 | 0.0098 | 0.52 ( 0.31, 0.86) | | 0.51 ( 0.30, 0.86) | | -0.02 (-0.04,-0.01) | |
| Europe | 1334 | 56 | 4.2 | 1361 | 42 | 3.1 | 0.1193 | 0.73 ( 0.49, 1.09) | | 0.72 ( 0.48, 1.09) | | -0.01 (-0.03, 0.00) | |
| Asia | 405 | 13 | 3.2 | 413 | 12 | 2.9 | 0.8360 | 0.92 ( 0.42, 2.01) | | 0.92 ( 0.41, 2.05) | | 0.00 (-0.03, 0.02) | |
| Other | 171 | 4 | 2.3 | 180 | 5 | 2.8 | 0.8053 | 1.18 ( 0.32, 4.32) | | 1.18 ( 0.31, 4.49) | | 0.00 (-0.03, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.8037 |
| Diabetic | 1739 | 73 | 4.2 | 1779 | 52 | 2.9 | 0.0399 | 0.70 ( 0.49, 0.99) | | 0.69 ( 0.48, 0.98) | | -0.01 (-0.03, 0.00) | |
| Non-Diabetic | 1536 | 75 | 4.9 | 1551 | 56 | 3.6 | 0.0795 | 0.74 ( 0.53, 1.04) | | 0.73 ( 0.51, 1.04) | | -0.01 (-0.03, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.3955 |
| <30 | 1975 | 77 | 3.9 | 1930 | 48 | 2.5 | 0.0120 | 0.64 ( 0.45, 0.91) | | 0.63 ( 0.44, 0.91) | | -0.01 (-0.03, 0.00) | |
| >=30 | 1300 | 71 | 5.5 | 1400 | 60 | 4.3 | 0.1616 | 0.79 ( 0.56, 1.10) | | 0.78 ( 0.55, 1.11) | | -0.01 (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.7112 |
| <130 | 1684 | 77 | 4.6 | 1687 | 53 | 3.1 | 0.0298 | 0.69 ( 0.49, 0.97) | | 0.67 ( 0.47, 0.96) | | -0.01 (-0.03, 0.00) | |
| >=130 | 1591 | 71 | 4.5 | 1643 | 55 | 3.3 | 0.1032 | 0.75 ( 0.53, 1.06) | | 0.74 ( 0.52, 1.06) | | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

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System organ class: Infections and infestations
Preferred term: Bronchitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.3831 |
| <75 | 1653 | 84 | 5.1 | 1612 | 59 | 3.7 | 0.0442 | 0.72 ( 0.52, | 0.99) | 0.71 ( 0.50, | 0.99) | -0.01 (-0.03, 0.00) | |
| 75 to <85 | 1005 | 37 | 3.7 | 1085 | 35 | 3.2 | 0.5705 | 0.88 ( 0.56, | 1.38) | 0.87 ( 0.55, | 1.40) | 0.00 (-0.02, 0.01) | |
| >=85 | 617 | 27 | 4.4 | 633 | 14 | 2.2 | 0.0316 | 0.51 ( 0.27, | 0.95) | 0.49 ( 0.26, | 0.95) | -0.02 (-0.04, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.6740 |
| <30 | 250 | 13 | 5.2 | 263 | 9 | 3.4 | 0.3152 | 0.66 ( 0.29, | 1.50) | 0.65 ( 0.27, | 1.53) | -0.02 (-0.05, 0.02) | |
| 30 to <45 | 898 | 38 | 4.2 | 909 | 33 | 3.6 | 0.4982 | 0.85 ( 0.54, | 1.35) | 0.85 ( 0.53, | 1.37) | -0.01 (-0.02, 0.01) | |
| >=45 | 2126 | 97 | 4.6 | 2158 | 66 | 3.1 | 0.0100 | 0.67 ( 0.49, | 0.91) | 0.66 ( 0.48, | 0.91) | -0.02 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.7064 |
| Normal (<30) | 1216 | 59 | 4.9 | 1243 | 45 | 3.6 | 0.1278 | 0.75 ( 0.51, | 1.09) | 0.74 ( 0.49, | 1.09) | -0.01 (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 61 | 3.9 | 1546 | 46 | 3.0 | 0.1401 | 0.75 ( 0.52, | 1.10) | 0.75 ( 0.51, | 1.10) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 500 | 27 | 5.4 | 525 | 16 | 3.0 | 0.0618 | 0.57 ( 0.31, | 1.04) | 0.55 ( 0.29, | 1.04) | -0.02 (-0.05, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.8471 |
| Low, moderate or high | 2430 | 112 | 4.6 | 2495 | 83 | 3.3 | 0.0202 | 0.72 ( 0.55, | 0.95) | 0.71 ( 0.53, | 0.95) | -0.01 (-0.02, 0.00) | |
| Very high | 834 | 36 | 4.3 | 820 | 24 | 2.9 | 0.1338 | 0.68 ( 0.41, | 1.13) | 0.67 ( 0.40, | 1.13) | -0.01 (-0.03, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.8221 |
| No | 572 | 30 | 5.2 | 578 | 23 | 4.0 | 0.3022 | 0.76 ( 0.44, | 1.29) | 0.75 ( 0.43, | 1.30) | -0.01 (-0.04, 0.01) | |
| Yes | 2703 | 118 | 4.4 | 2752 | 85 | 3.1 | 0.0122 | 0.71 ( 0.54, | 0.93) | 0.70 ( 0.52, | 0.93) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.3109 |
| No | 344 | 20 | 5.8 | 349 | 10 | 2.9 | 0.0623 | 0.50 ( 0.24, | 1.05) | 0.48 ( 0.22, | 1.05) | -0.03 (-0.06, 0.00) | |
| Yes | 2931 | 128 | 4.4 | 2981 | 98 | 3.3 | 0.0297 | 0.75 ( 0.58, | 0.97) | 0.74 ( 0.57, | 0.97) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Bronchitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.8521 |
| No | 275 | 8 | 2.9 | 307 | 7 | 2.3 | 0.6217 | 0.79 ( 0.30, 2.05) | 0.78 ( 0.29, 2.10) | -0.01 (-0.03, 0.02) | |
| Yes | 3000 | 140 | 4.7 | 3023 | 101 | 3.3 | 0.0084 | 0.72 ( 0.56, 0.92) | 0.71 ( 0.54, 0.92) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: COVID-19

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 105 | 3.2 | 3330 | 98 | 2.9 | 0.4951 | 0.91 ( 0.70, 1.19) | 0.91 ( 0.68, 1.20) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Influenza

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 82 | 2.5 | 3330 | 62 | 1.9 | 0.0729 | 0.74 ( 0.54, 1.03) | 0.74 ( 0.53, 1.03) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Cellulitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 54 | 1.6 | 3330 | 65 | 2.0 | 0.3642 | 1.18 ( 0.83, 1.69) | 1.18 ( 0.82, 1.70) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Cystitis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 48 | 1.5 | 3330 | 41 | 1.2 | 0.3960 | 0.84 ( 0.55, 1.26) | 0.83 ( 0.55, 1.27) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Gastroenteritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 47 | 1.4 | 3330 | 46 | 1.4 | 0.8449 | 0.96 ( 0.64, 1.44) | 0.96 ( 0.64, 1.45) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Herpes zoster

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 38 | 1.2 | 3330 | 45 | 1.4 | 0.4882 | 1.16 ( 0.76, 1.79) | 1.17 ( 0.76, 1.80) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Sepsis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 35 | 1.1 | 3330 | 42 | 1.3 | 0.4735 | 1.18 ( 0.75, 1.84) | 1.18 ( 0.75, 1.85) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperkalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 296 | 9.0 | 3330 | 251 | 7.5 | 0.0265 | 0.83 ( 0.71, | 0.98) | 0.82 ( 0.69, | 0.98) | -0.02 (-0.03, 0.00) | |
| Study | | | | | | | | | | | | | 0.6869 |
| 1245.110 | 2001 | 186 | 9.3 | 2052 | 163 | 7.9 | 0.1251 | 0.85 ( 0.70, | 1.04) | 0.84 ( 0.68, | 1.05) | -0.01 (-0.03, 0.00) | |
| 1245.121 | 1274 | 110 | 8.6 | 1278 | 88 | 6.9 | 0.0988 | 0.80 ( 0.61, | 1.04) | 0.78 ( 0.58, | 1.05) | -0.02 (-0.04, 0.00) | |
| Sex | | | | | | | | | | | | | 0.1598 |
| Male | 2023 | 177 | 8.7 | 2068 | 165 | 8.0 | 0.3714 | 0.91 ( 0.74, | 1.12) | 0.90 ( 0.72, | 1.13) | -0.01 (-0.02, 0.01) | |
| Female | 1252 | 119 | 9.5 | 1262 | 86 | 6.8 | 0.0138 | 0.72 ( 0.55, | 0.94) | 0.70 ( 0.52, | 0.93) | -0.03 (-0.05,-0.01) | |
| Age [years] | | | | | | | | | | | | | 0.5712 |
| <65 | 766 | 69 | 9.0 | 705 | 58 | 8.2 | 0.5648 | 0.91 ( 0.65, | 1.26) | 0.90 ( 0.62, | 1.30) | -0.01 (-0.04, 0.02) | |
| >=65 | 2509 | 227 | 9.0 | 2625 | 193 | 7.4 | 0.0267 | 0.81 ( 0.68, | 0.98) | 0.80 ( 0.65, | 0.97) | -0.02 (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | 0.1581 |
| North America | 434 | 31 | 7.1 | 432 | 42 | 9.7 | 0.1732 | 1.36 ( 0.87, | 2.12) | 1.40 ( 0.86, | 2.27) | 0.03 (-0.01, 0.06) | |
| Latin America | 931 | 103 | 11.1 | 944 | 79 | 8.4 | 0.0526 | 0.76 ( 0.58, | >1.00) | 0.74 ( 0.54, | 1.00) | -0.03 (-0.05, 0.00) | |
| Europe | 1334 | 100 | 7.5 | 1361 | 81 | 6.0 | 0.1106 | 0.79 ( 0.60, | 1.05) | 0.78 ( 0.58, | 1.06) | -0.02 (-0.03, 0.00) | |
| Asia | 405 | 42 | 10.4 | 413 | 28 | 6.8 | 0.0678 | 0.65 ( 0.41, | 1.04) | 0.63 ( 0.38, | 1.04) | -0.04 (-0.07, 0.00) | |
| Other | 171 | 20 | 11.7 | 180 | 21 | 11.7 | 0.9794 | 0.99 ( 0.56, | 1.77) | 0.99 ( 0.52, | 1.90) | 0.00 (-0.07, 0.07) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.3988 |
| Diabetic | 1739 | 194 | 11.2 | 1779 | 157 | 8.8 | 0.0202 | 0.79 ( 0.65, | 0.96) | 0.77 ( 0.62, | 0.96) | -0.02 (-0.04, 0.00) | |
| Non-Diabetic | 1536 | 102 | 6.6 | 1551 | 94 | 6.1 | 0.5108 | 0.91 ( 0.70, | 1.20) | 0.91 ( 0.68, | 1.21) | -0.01 (-0.02, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.9372 |
| <30 | 1975 | 179 | 9.1 | 1930 | 147 | 7.6 | 0.1002 | 0.84 ( 0.68, | 1.03) | 0.83 ( 0.66, | 1.04) | -0.01 (-0.03, 0.00) | |
| >=30 | 1300 | 117 | 9.0 | 1400 | 104 | 7.4 | 0.1442 | 0.83 ( 0.64, | 1.07) | 0.81 ( 0.62, | 1.07) | -0.02 (-0.04, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.1917 |
| <130 | 1684 | 150 | 8.9 | 1687 | 112 | 6.6 | 0.0127 | 0.74 ( 0.59, | 0.94) | 0.72 ( 0.56, | 0.93) | -0.02 (-0.04, 0.00) | |
| >=130 | 1591 | 146 | 9.2 | 1643 | 139 | 8.5 | 0.4668 | 0.92 ( 0.74, | 1.15) | 0.91 ( 0.72, | 1.17) | -0.01 (-0.03, 0.01) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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System organ class: Metabolism and nutrition disorders
Preferred term: Hyperkalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.6304 |
| <75 | 1653 | 166 | 10.0 | 1612 | 143 | 8.9 | 0.2467 | 0.88 ( 0.71, | 1.09) | 0.87 ( 0.69, | 1.10) | -0.01 (-0.03, 0.01) | |
| 75 to <85 | 1005 | 82 | 8.2 | 1085 | 65 | 6.0 | 0.0541 | 0.74 ( 0.54, | 1.01) | 0.72 ( 0.51, | 1.01) | -0.02 (-0.04, 0.00) | |
| >=85 | 617 | 48 | 7.8 | 633 | 43 | 6.8 | 0.4990 | 0.87 ( 0.59, | 1.30) | 0.86 ( 0.56, | 1.32) | -0.01 (-0.04, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.7170 |
| <30 | 250 | 38 | 15.2 | 263 | 32 | 12.2 | 0.3148 | 0.80 ( 0.52, | 1.24) | 0.77 ( 0.46, | 1.28) | -0.03 (-0.09, 0.03) | |
| 30 to <45 | 898 | 114 | 12.7 | 909 | 89 | 9.8 | 0.0502 | 0.77 ( 0.59, | >1.00) | 0.75 ( 0.56, | 1.00) | -0.03 (-0.06, 0.00) | |
| >=45 | 2126 | 144 | 6.8 | 2158 | 130 | 6.0 | 0.3072 | 0.89 ( 0.71, | 1.12) | 0.88 ( 0.69, | 1.12) | -0.01 (-0.02, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.3726 |
| Normal (<30) | 1216 | 115 | 9.5 | 1243 | 84 | 6.8 | 0.0143 | 0.71 ( 0.55, | 0.94) | 0.69 ( 0.52, | 0.93) | -0.03 (-0.05,-0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 121 | 7.8 | 1546 | 111 | 7.2 | 0.4954 | 0.92 ( 0.72, | 1.18) | 0.91 ( 0.70, | 1.19) | -0.01 (-0.03, 0.01) | |
| Macroalbuminuria (>300) | 500 | 59 | 11.8 | 525 | 55 | 10.5 | 0.5240 | 0.89 ( 0.63, | 1.26) | 0.88 ( 0.60, | 1.30) | -0.01 (-0.05, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.9967 |
| Low, moderate or high | 2430 | 179 | 7.4 | 2495 | 154 | 6.2 | 0.0930 | 0.84 ( 0.68, | 1.03) | 0.83 ( 0.66, | 1.03) | -0.01 (-0.03, 0.00) | |
| Very high | 834 | 117 | 14.0 | 820 | 96 | 11.7 | 0.1635 | 0.84 ( 0.65, | 1.08) | 0.81 ( 0.61, | 1.09) | -0.02 (-0.06, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.6934 |
| No | 572 | 45 | 7.9 | 578 | 35 | 6.1 | 0.2275 | 0.77 ( 0.50, | 1.18) | 0.75 ( 0.48, | 1.19) | -0.02 (-0.05, 0.01) | |
| Yes | 2703 | 251 | 9.3 | 2752 | 216 | 7.8 | 0.0562 | 0.84 ( 0.71, | >1.00) | 0.83 ( 0.69, | 1.01) | -0.01 (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.5753 |
| No | 344 | 35 | 10.2 | 349 | 26 | 7.4 | 0.2052 | 0.73 ( 0.45, | 1.19) | 0.71 ( 0.42, | 1.21) | -0.03 (-0.07, 0.01) | |
| Yes | 2931 | 261 | 8.9 | 2981 | 225 | 7.5 | 0.0561 | 0.85 ( 0.71, | >1.00) | 0.83 ( 0.69, | 1.00) | -0.01 (-0.03, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

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System organ class: Metabolism and nutrition disorders
Preferred term: Hyperkalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.0410 |
| No | 275 | 16 | 5.8 | 307 | 27 | 8.8 | 0.1692 | 1.52 ( 0.83, 2.75) | 1.57 ( 0.82, 2.97) | 0.03 (-0.01, 0.07) | |
| Yes | 3000 | 280 | 9.3 | 3023 | 224 | 7.4 | 0.0069 | 0.79 ( 0.67, 0.94) | 0.78 ( 0.65, 0.93) | -0.02 (-0.03,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperuricaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 237 | 7.2 | 3330 | 162 | 4.9 | <0.0001 | 0.67 | ( 0.55, 0.82) | 0.65 | ( 0.53, 0.80) | -0.02 | (-0.04,-0.01) | |
| Study | | | | | | | | | | | | | | 0.0481 |
| 1245.110 | 2001 | 148 | 7.4 | 2052 | 117 | 5.7 | 0.0291 | 0.77 | ( 0.61, 0.97) | 0.76 | ( 0.59, 0.97) | -0.02 | (-0.03, 0.00) | |
| 1245.121 | 1274 | 89 | 7.0 | 1278 | 45 | 3.5 | <0.0001 | 0.50 | ( 0.36, 0.72) | 0.49 | ( 0.34, 0.70) | -0.03 | (-0.05,-0.02) | |
| Sex | | | | | | | | | | | | | | 0.8801 |
| Male | 2023 | 143 | 7.1 | 2068 | 97 | 4.7 | 0.0012 | 0.66 | ( 0.52, 0.85) | 0.65 | ( 0.50, 0.84) | -0.02 | (-0.04,-0.01) | |
| Female | 1252 | 94 | 7.5 | 1262 | 65 | 5.2 | 0.0144 | 0.68 | ( 0.50, 0.93) | 0.67 | ( 0.48, 0.92) | -0.02 | (-0.04, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.0351 |
| <65 | 766 | 74 | 9.7 | 705 | 62 | 8.8 | 0.5512 | 0.91 | ( 0.66, 1.25) | 0.90 | ( 0.63, 1.28) | -0.01 | (-0.04, 0.02) | |
| >=65 | 2509 | 163 | 6.5 | 2625 | 100 | 3.8 | <0.0001 | 0.59 | ( 0.46, 0.75) | 0.57 | ( 0.44, 0.74) | -0.03 | (-0.04,-0.01) | |
| Region | | | | | | | | | | | | | | 0.6502 |
| North America | 434 | 8 | 1.8 | 432 | 6 | 1.4 | 0.6026 | 0.77 | ( 0.28, 2.10) | 0.76 | ( 0.27, 2.14) | 0.00 | (-0.02, 0.01) | |
| Latin America | 931 | 114 | 12.2 | 944 | 78 | 8.3 | 0.0051 | 0.68 | ( 0.52, 0.89) | 0.65 | ( 0.48, 0.88) | -0.04 | (-0.07,-0.01) | |
| Europe | 1334 | 72 | 5.4 | 1361 | 45 | 3.3 | 0.0075 | 0.61 | ( 0.42, 0.88) | 0.60 | ( 0.41, 0.87) | -0.02 | (-0.04,-0.01) | |
| Asia | 405 | 36 | 8.9 | 413 | 23 | 5.6 | 0.0735 | 0.63 | ( 0.38, 1.05) | 0.61 | ( 0.36, 1.05) | -0.03 | (-0.07, 0.00) | |
| Other | 171 | 7 | 4.1 | 180 | 10 | 5.6 | 0.5333 | 1.35 | ( 0.52, 3.47) | 1.37 | ( 0.51, 3.69) | 0.01 | (-0.03, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0290 |
| Diabetic | 1739 | 129 | 7.4 | 1779 | 106 | 6.0 | 0.0813 | 0.80 | ( 0.63, 1.03) | 0.79 | ( 0.61, 1.03) | -0.01 | (-0.03, 0.00) | |
| Non-Diabetic | 1536 | 108 | 7.0 | 1551 | 56 | 3.6 | <0.0001 | 0.51 | ( 0.37, 0.70) | 0.49 | ( 0.36, 0.69) | -0.03 | (-0.05,-0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2942 |
| <30 | 1975 | 136 | 6.9 | 1930 | 81 | 4.2 | 0.0002 | 0.61 | ( 0.46, 0.79) | 0.59 | ( 0.44, 0.78) | -0.03 | (-0.04,-0.01) | |
| >=30 | 1300 | 101 | 7.8 | 1400 | 81 | 5.8 | 0.0416 | 0.75 | ( 0.56, 0.99) | 0.73 | ( 0.54, 0.99) | -0.02 | (-0.04, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8387 |
| <130 | 1684 | 119 | 7.1 | 1687 | 82 | 4.9 | 0.0062 | 0.68 | ( 0.52, 0.90) | 0.67 | ( 0.50, 0.89) | -0.02 | (-0.04,-0.01) | |
| >=130 | 1591 | 118 | 7.4 | 1643 | 80 | 4.9 | 0.0026 | 0.66 | ( 0.50, 0.87) | 0.64 | ( 0.48, 0.86) | -0.03 | (-0.04,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperuricaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.4421 |
| <75 | 1653 | 130 | 7.9 | 1612 | 78 | 4.8 | 0.0003 | 0.61 ( 0.47, | 0.80) | 0.59 ( 0.44, | 0.79) | -0.03 (-0.05,-0.01) | |
| 75 to <85 | 1005 | 66 | 6.6 | 1085 | 48 | 4.4 | 0.0319 | 0.67 ( 0.47, | 0.97) | 0.66 ( 0.45, | 0.97) | -0.02 (-0.04, 0.00) | |
| >=85 | 617 | 41 | 6.6 | 633 | 36 | 5.7 | 0.4745 | 0.85 ( 0.55, | 1.32) | 0.85 ( 0.53, | 1.34) | -0.01 (-0.04, 0.02) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.3205 |
| <30 | 250 | 25 | 10.0 | 263 | 24 | 9.1 | 0.9438 | 0.98 ( 0.58, | 1.66) | 0.98 ( 0.54, | 1.77) | 0.00 (-0.05, 0.05) | |
| 30 to <45 | 898 | 69 | 7.7 | 909 | 47 | 5.2 | 0.0281 | 0.67 ( 0.47, | 0.96) | 0.65 ( 0.44, | 0.96) | -0.03 (-0.05, 0.00) | |
| >=45 | 2126 | 143 | 6.7 | 2158 | 91 | 4.2 | 0.0003 | 0.63 ( 0.48, | 0.81) | 0.61 ( 0.47, | 0.80) | -0.03 (-0.04,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.0356 |
| Normal (<30) | 1216 | 87 | 7.2 | 1243 | 47 | 3.8 | 0.0002 | 0.53 ( 0.37, | 0.75) | 0.51 ( 0.35, | 0.73) | -0.03 (-0.05,-0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 109 | 7.0 | 1546 | 70 | 4.5 | 0.0027 | 0.64 ( 0.48, | 0.86) | 0.63 ( 0.46, | 0.85) | -0.03 (-0.04,-0.01) | |
| Macroalbuminuria (>300) | 500 | 40 | 8.0 | 525 | 44 | 8.4 | 0.7920 | 1.06 ( 0.70, | 1.59) | 1.06 ( 0.68, | 1.66) | 0.00 (-0.03, 0.04) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.1623 |
| Low, moderate or high | 2430 | 164 | 6.7 | 2495 | 103 | 4.1 | <0.0001 | 0.61 ( 0.48, | 0.78) | 0.59 ( 0.46, | 0.77) | -0.03 (-0.04,-0.01) | |
| Very high | 834 | 73 | 8.8 | 820 | 58 | 7.1 | 0.2270 | 0.82 ( 0.59, | 1.14) | 0.80 ( 0.56, | 1.15) | -0.02 (-0.04, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.1387 |
| No | 572 | 44 | 7.7 | 578 | 21 | 3.6 | 0.0029 | 0.47 ( 0.28, | 0.78) | 0.45 ( 0.27, | 0.77) | -0.04 (-0.07,-0.01) | |
| Yes | 2703 | 193 | 7.1 | 2752 | 141 | 5.1 | 0.0018 | 0.72 ( 0.58, | 0.88) | 0.70 ( 0.56, | 0.88) | -0.02 (-0.03,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.4386 |
| No | 344 | 22 | 6.4 | 349 | 19 | 5.4 | 0.5672 | 0.84 ( 0.46, | 1.53) | 0.83 ( 0.44, | 1.57) | -0.01 (-0.05, 0.02) | |
| Yes | 2931 | 215 | 7.3 | 2981 | 143 | 4.8 | <0.0001 | 0.65 ( 0.53, | 0.80) | 0.63 ( 0.51, | 0.79) | -0.03 (-0.04,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperuricaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.4757 |
| No | 275 | 10 | 3.6 | 307 | 5 | 1.6 | 0.1358 | 0.47 ( 0.17, 1.30) | 0.46 ( 0.16, 1.31) | -0.02 (-0.05, 0.01) | |
| Yes | 3000 | 227 | 7.6 | 3023 | 157 | 5.2 | 0.0002 | 0.69 ( 0.56, 0.83) | 0.67 ( 0.54, 0.82) | -0.02 (-0.04,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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System organ class: Metabolism and nutrition disorders
Preferred term: Diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 197 | 6.0 | 3330 | 170 | 5.1 | 0.0966 | 0.85 ( 0.69, 1.03) | 0.84 ( 0.68, 1.03) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Gout

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 123 | 3.8 | 3330 | 91 | 2.7 | 0.0188 | 0.73 | ( 0.56, 0.95) | 0.72 | ( 0.55, 0.95) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.4363 |
| 1245.110 | 2001 | 80 | 4.0 | 2052 | 55 | 2.7 | 0.0194 | 0.67 | ( 0.48, 0.94) | 0.66 | ( 0.47, 0.94) | -0.01 | (-0.02, 0.00) | |
| 1245.121 | 1274 | 43 | 3.4 | 1278 | 36 | 2.8 | 0.4156 | 0.83 | ( 0.54, 1.29) | 0.83 | ( 0.53, 1.30) | -0.01 | (-0.02, 0.01) | |
| Sex | | | | | | | | | | | | | | 0.0017 |
| Male | 2023 | 80 | 4.0 | 2068 | 77 | 3.7 | 0.6997 | 0.94 | ( 0.69, 1.28) | 0.94 | ( 0.68, 1.29) | 0.00 | (-0.01, 0.01) | |
| Female | 1252 | 43 | 3.4 | 1262 | 14 | 1.1 | <0.0001 | 0.32 | ( 0.18, 0.58) | 0.31 | ( 0.17, 0.57) | -0.02 | (-0.04,-0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.8661 |
| <65 | 766 | 28 | 3.7 | 705 | 18 | 2.6 | 0.2184 | 0.69 | ( 0.39, 1.25) | 0.69 | ( 0.38, 1.25) | -0.01 | (-0.03, 0.01) | |
| >=65 | 2509 | 95 | 3.8 | 2625 | 73 | 2.8 | 0.0429 | 0.73 | ( 0.54, 0.99) | 0.73 | ( 0.53, 0.99) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | 0.6832 |
| North America | 434 | 30 | 6.9 | 432 | 25 | 5.8 | 0.4962 | 0.84 | ( 0.50, 1.40) | 0.83 | ( 0.48, 1.43) | -0.01 | (-0.04, 0.02) | |
| Latin America | 931 | 15 | 1.6 | 944 | 8 | 0.8 | 0.1404 | 0.53 | ( 0.23, 1.25) | 0.53 | ( 0.22, 1.25) | -0.01 | (-0.02, 0.00) | |
| Europe | 1334 | 43 | 3.2 | 1361 | 37 | 2.7 | 0.4527 | 0.85 | ( 0.55, 1.31) | 0.84 | ( 0.54, 1.32) | 0.00 | (-0.02, 0.01) | |
| Asia | 405 | 18 | 4.4 | 413 | 12 | 2.9 | 0.2585 | 0.66 | ( 0.32, 1.37) | 0.65 | ( 0.31, 1.37) | -0.01 | (-0.04, 0.01) | |
| Other | 171 | 17 | 9.9 | 180 | 9 | 5.0 | 0.0657 | 0.50 | ( 0.24, 1.06) | 0.47 | ( 0.21, 1.07) | -0.05 | (-0.11, 0.00) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.7406 |
| Diabetic | 1739 | 59 | 3.4 | 1779 | 46 | 2.6 | 0.1591 | 0.76 | ( 0.52, 1.11) | 0.76 | ( 0.51, 1.12) | -0.01 | (-0.02, 0.00) | |
| Non-Diabetic | 1536 | 64 | 4.2 | 1551 | 45 | 2.9 | 0.0567 | 0.70 | ( 0.48, 1.01) | 0.69 | ( 0.47, 1.01) | -0.01 | (-0.03, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.9991 |
| <30 | 1975 | 77 | 3.9 | 1930 | 55 | 2.8 | 0.0710 | 0.73 | ( 0.52, 1.03) | 0.72 | ( 0.51, 1.03) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1300 | 46 | 3.5 | 1400 | 36 | 2.6 | 0.1537 | 0.73 | ( 0.48, 1.13) | 0.73 | ( 0.47, 1.13) | -0.01 | (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7341 |
| <130 | 1684 | 71 | 4.2 | 1687 | 54 | 3.2 | 0.1159 | 0.76 | ( 0.54, 1.07) | 0.75 | ( 0.52, 1.08) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1591 | 52 | 3.3 | 1643 | 37 | 2.3 | 0.0784 | 0.69 | ( 0.46, 1.05) | 0.68 | ( 0.45, 1.05) | -0.01 | (-0.02, 0.00) | |

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System organ class: Metabolism and nutrition disorders
Preferred term: Gout

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.2118 |
| <75 | 1653 | 69 | 4.2 | 1612 | 60 | 3.7 | 0.5104 | 0.89 ( 0.64, | 1.25) | 0.89 ( 0.62, | 1.26) | 0.00 (-0.02, 0.01) | |
| 75 to <85 | 1005 | 32 | 3.2 | 1085 | 19 | 1.8 | 0.0352 | 0.55 ( 0.32, | 0.97) | 0.54 ( 0.31, | 0.97) | -0.01 (-0.03, 0.00) | |
| >=85 | 617 | 22 | 3.6 | 633 | 12 | 1.9 | 0.0682 | 0.53 ( 0.26, | 1.06) | 0.52 ( 0.26, | 1.06) | -0.02 (-0.03, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.0498 |
| <30 | 250 | 10 | 4.0 | 263 | 18 | 6.8 | 0.1489 | 1.74 ( 0.81, | 3.76) | 1.79 ( 0.81, | 3.95) | 0.03 (-0.01, 0.07) | |
| 30 to <45 | 898 | 52 | 5.8 | 909 | 31 | 3.4 | 0.0158 | 0.59 ( 0.38, | 0.91) | 0.57 ( 0.36, | 0.91) | -0.02 (-0.04, 0.00) | |
| >=45 | 2126 | 61 | 2.9 | 2158 | 42 | 1.9 | 0.0477 | 0.68 ( 0.46, | <1.00) | 0.67 ( 0.45, | 1.00) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.2522 |
| Normal (<30) | 1216 | 52 | 4.3 | 1243 | 33 | 2.7 | 0.0275 | 0.62 ( 0.40, | 0.95) | 0.61 ( 0.39, | 0.95) | -0.02 (-0.03, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 58 | 3.7 | 1546 | 41 | 2.7 | 0.0839 | 0.71 ( 0.48, | 1.05) | 0.70 ( 0.47, | 1.05) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 500 | 13 | 2.6 | 525 | 17 | 3.2 | 0.5425 | 1.25 ( 0.61, | 2.53) | 1.25 ( 0.60, | 2.61) | 0.01 (-0.01, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.0995 |
| Low, moderate or high | 2430 | 81 | 3.3 | 2495 | 51 | 2.0 | 0.0050 | 0.61 ( 0.43, | 0.87) | 0.60 ( 0.42, | 0.86) | -0.01 (-0.02, 0.00) | |
| Very high | 834 | 42 | 5.0 | 820 | 40 | 4.9 | 0.8850 | 0.97 ( 0.64, | 1.48) | 0.97 ( 0.62, | 1.51) | 0.00 (-0.02, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.9954 |
| No | 572 | 34 | 5.9 | 578 | 25 | 4.3 | 0.2126 | 0.73 ( 0.44, | 1.20) | 0.71 ( 0.42, | 1.21) | -0.02 (-0.04, 0.01) | |
| Yes | 2703 | 89 | 3.3 | 2752 | 66 | 2.4 | 0.0465 | 0.73 ( 0.53, | <1.00) | 0.72 ( 0.52, | 1.00) | -0.01 (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.9293 |
| No | 344 | 10 | 2.9 | 349 | 7 | 2.0 | 0.4592 | 0.70 ( 0.27, | 1.82) | 0.69 ( 0.26, | 1.84) | -0.01 (-0.03, 0.01) | |
| Yes | 2931 | 113 | 3.9 | 2981 | 84 | 2.8 | 0.0260 | 0.73 ( 0.55, | 0.96) | 0.72 ( 0.54, | 0.96) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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System organ class: Metabolism and nutrition disorders
Preferred term: Gout

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.9361 |
| No | 275 | 4 | 1.5 | 307 | 3 | 1.0 | 0.6000 | 0.69 ( 0.17, 2.75) | 0.69 ( 0.17, 2.80) | -0.01 (-0.02, 0.01) | |
| Yes | 3000 | 119 | 4.0 | 3023 | 88 | 2.9 | 0.0242 | 0.73 ( 0.56, 0.96) | 0.73 ( 0.55, 0.96) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypoglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 116 | 3.5 | 3330 | 115 | 3.5 | 0.8307 | 0.97 ( 0.76, 1.25) | 0.97 ( 0.75, 1.26) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypokalaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 87 | 2.7 | 3330 | 105 | 3.2 | 0.2352 | 1.18 ( 0.90, 1.57) | 1.19 ( 0.89, 1.59) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Dehydration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 60 | 1.8 | 3330 | 77 | 2.3 | 0.1752 | 1.26 ( 0.90, 1.76) | 1.27 ( 0.90, 1.78) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Type 2 diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Overall | 3275 | 66 | 2.0 | 3330 | 42 | 1.3 | 0.0164 | 0.63 ( 0.43, 0.92) | 0.62 ( 0.42, 0.92) | -0.01 (-0.01, 0.00) | | |
| Study | | | | | | | | | | | | 0.4319 |
| 1245.110 | 2001 | 33 | 1.6 | 2052 | 18 | 0.9 | 0.0275 | 0.53 ( 0.30, 0.94) | 0.53 ( 0.30, 0.94) | -0.01 (-0.01, 0.00) | | |
| 1245.121 | 1274 | 33 | 2.6 | 1278 | 24 | 1.9 | 0.2235 | 0.72 ( 0.43, 1.22) | 0.72 ( 0.42, 1.22) | -0.01 (-0.02, 0.00) | | |
| Sex | | | | | | | | | | | | 0.6776 |
| Male | 2023 | 41 | 2.0 | 2068 | 28 | 1.4 | 0.0956 | 0.67 ( 0.42, 1.08) | 0.66 ( 0.41, 1.08) | -0.01 (-0.01, 0.00) | | |
| Female | 1252 | 25 | 2.0 | 1262 | 14 | 1.1 | 0.0772 | 0.56 ( 0.30, 1.07) | 0.56 ( 0.29, 1.08) | -0.01 (-0.02, 0.00) | | |
| Age [years] | | | | | | | | | | | | 0.2339 |
| <65 | 766 | 20 | 2.6 | 705 | 16 | 2.3 | 0.6974 | 0.88 ( 0.46, 1.68) | 0.88 ( 0.45, 1.71) | 0.00 (-0.02, 0.01) | | |
| >=65 | 2509 | 46 | 1.8 | 2625 | 26 | 1.0 | 0.0102 | 0.54 ( 0.33, 0.87) | 0.54 ( 0.33, 0.87) | -0.01 (-0.01, 0.00) | | |
| Region | | | | | | | | | | | | 0.2182 |
| North America | 434 | 5 | 1.2 | 432 | 7 | 1.6 | 0.5507 | 1.41 ( 0.45, 4.40) | 1.42 ( 0.45, 4.52) | 0.00 (-0.01, 0.02) | | |
| Latin America | 931 | 25 | 2.7 | 944 | 11 | 1.2 | 0.0155 | 0.43 ( 0.21, 0.87) | 0.42 ( 0.21, 0.87) | -0.02 (-0.03, 0.00) | | |
| Europe | 1334 | 27 | 2.0 | 1361 | 14 | 1.0 | 0.0353 | 0.51 ( 0.27, 0.97) | 0.50 ( 0.26, 0.97) | -0.01 (-0.02, 0.00) | | |
| Asia | 405 | 9 | 2.2 | 413 | 8 | 1.9 | 0.8328 | 0.90 ( 0.35, 2.31) | 0.90 ( 0.34, 2.37) | 0.00 (-0.02, 0.02) | | |
| Other | 171 | 0 | 0 | 180 | 2 | 1.1 | 0.3429 | 2.87 ( 0.29, 28.17) | 2.90 ( 0.29, 28.55) | 0.01 (-0.01, 0.03) | | |
| Baseline Diabetes Status | | | | | | | | | | | | 0.5726 |
| Diabetic | 1739 | 34 | 2.0 | 1779 | 24 | 1.3 | 0.1661 | 0.70 ( 0.41, 1.17) | 0.69 ( 0.41, 1.17) | -0.01 (-0.01, 0.00) | | |
| Non-Diabetic | 1536 | 32 | 2.1 | 1551 | 18 | 1.2 | 0.0422 | 0.56 ( 0.31, 0.99) | 0.55 ( 0.31, 0.99) | -0.01 (-0.02, 0.00) | | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | 0.2308 |
| <30 | 1975 | 47 | 2.4 | 1930 | 24 | 1.2 | 0.0084 | 0.53 ( 0.32, 0.86) | 0.52 ( 0.32, 0.85) | -0.01 (-0.02, 0.00) | | |
| >=30 | 1300 | 19 | 1.5 | 1400 | 18 | 1.3 | 0.6458 | 0.86 ( 0.45, 1.64) | 0.86 ( 0.45, 1.65) | 0.00 (-0.01, 0.01) | | |
| Baseline SBP [mmHg] | | | | | | | | | | | | 0.5992 |
| <130 | 1684 | 34 | 2.0 | 1687 | 19 | 1.1 | 0.0399 | 0.56 ( 0.32, 0.98) | 0.56 ( 0.32, 0.98) | -0.01 (-0.02, 0.00) | | |
| >=130 | 1591 | 32 | 2.0 | 1643 | 23 | 1.4 | 0.1709 | 0.69 ( 0.41, 1.18) | 0.69 ( 0.40, 1.18) | -0.01 (-0.02, 0.00) | | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Type 2 diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.5125 |
| <75 | 1653 | 30 | 1.8 | 1612 | 15 | 0.9 | 0.0311 | 0.51 | ( 0.28, | 0.95) | 0.51 ( 0.27, | 0.95) | -0.01 (-0.02, 0.00) | |
| 75 to <85 | 1005 | 22 | 2.2 | 1085 | 14 | 1.3 | 0.1106 | 0.59 | ( 0.30, | 1.14) | 0.58 ( 0.29, | 1.14) | -0.01 (-0.02, 0.00) | |
| >=85 | 617 | 14 | 2.3 | 633 | 13 | 2.1 | 0.7791 | 0.90 | ( 0.43, | 1.89) | 0.90 ( 0.42, | 1.93) | 0.00 (-0.02, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6125 |
| <30 | 250 | 3 | 1.2 | 263 | 4 | 1.5 | 0.8138 | 1.20 | ( 0.26, | 5.59) | 1.21 ( 0.26, | 5.59) | 0.00 (-0.02, 0.02) | |
| 30 to <45 | 898 | 16 | 1.8 | 909 | 8 | 0.9 | 0.0973 | 0.50 | ( 0.21, | 1.15) | 0.49 ( 0.21, | 1.16) | -0.01 (-0.02, 0.00) | |
| >=45 | 2126 | 47 | 2.2 | 2158 | 30 | 1.4 | 0.0467 | 0.63 | ( 0.40, | <1.00) | 0.63 ( 0.40, | 1.00) | -0.01 (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.8724 |
| Normal (<30) | 1216 | 22 | 1.8 | 1243 | 13 | 1.0 | 0.1090 | 0.58 | ( 0.29, | 1.14) | 0.57 ( 0.29, | 1.14) | -0.01 (-0.02, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 29 | 1.9 | 1546 | 20 | 1.3 | 0.2091 | 0.70 | ( 0.40, | 1.23) | 0.69 ( 0.39, | 1.23) | -0.01 (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 500 | 15 | 3.0 | 525 | 9 | 1.7 | 0.1550 | 0.56 | ( 0.25, | 1.26) | 0.55 ( 0.24, | 1.27) | -0.01 (-0.03, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.8676 |
| Low, moderate or high | 2430 | 51 | 2.1 | 2495 | 32 | 1.3 | 0.0279 | 0.61 | ( 0.40, | 0.95) | 0.61 ( 0.39, | 0.95) | -0.01 (-0.02, 0.00) | |
| Very high | 834 | 15 | 1.8 | 820 | 10 | 1.2 | 0.3093 | 0.66 | ( 0.30, | 1.47) | 0.66 ( 0.29, | 1.48) | -0.01 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.1555 |
| No | 572 | 11 | 1.9 | 578 | 3 | 0.5 | 0.0279 | 0.27 | ( 0.07, | 0.95) | 0.26 ( 0.07, | 0.94) | -0.01 (-0.03, 0.00) | |
| Yes | 2703 | 55 | 2.0 | 2752 | 39 | 1.4 | 0.0830 | 0.70 | ( 0.47, | 1.05) | 0.69 ( 0.46, | 1.05) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9094 |
| No | 344 | 3 | 0.9 | 349 | 2 | 0.6 | 0.6488 | 0.69 | ( 0.14, | 3.42) | 0.69 ( 0.14, | 3.49) | 0.00 (-0.02, 0.01) | |
| Yes | 2931 | 63 | 2.1 | 2981 | 40 | 1.3 | 0.0188 | 0.63 | ( 0.42, | 0.93) | 0.62 ( 0.42, | 0.93) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Type 2 diabetes mellitus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.4059 |
| No | 275 | 2 | 0.7 | 307 | 3 | 1.0 | 0.8005 | 1.23 ( 0.24, 6.26) | 1.24 ( 0.24, 6.35) | 0.00 (-0.01, 0.02) | |
| Yes | 3000 | 64 | 2.1 | 3023 | 39 | 1.3 | 0.0121 | 0.61 ( 0.41, 0.90) | 0.60 ( 0.40, 0.90) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyperglycaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 41 | 1.3 | 3330 | 51 | 1.5 | 0.3349 | 1.22 ( 0.81, 1.84) | 1.23 ( 0.81, 1.85) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hyponatraemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 48 | 1.5 | 3330 | 38 | 1.1 | 0.2417 | 0.78 ( 0.51, 1.19) | 0.77 ( 0.50, 1.19) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Decreased appetite

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 38 | 1.2 | 3330 | 27 | 0.8 | 0.1491 | 0.70 ( 0.43, 1.14) | 0.70 ( 0.42, 1.14) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypertriglyceridaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 37 | 1.1 | 3330 | 34 | 1.0 | 0.6650 | 0.90 ( 0.57, 1.44) | 0.90 ( 0.56, 1.44) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypomagnesaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 34 | 1.0 | 3330 | 13 | 0.4 | 0.0016 | 0.37 | ( 0.20, 0.71) | 0.37 | ( 0.20, 0.71) | -0.01 | (-0.01, 0.00) | |
| Study | | | | | | | | | | | | | | 0.8729 |
| 1245.110 | 2001 | 28 | 1.4 | 2052 | 11 | 0.5 | 0.0049 | 0.38 | ( 0.19, 0.77) | 0.38 | ( 0.19, 0.76) | -0.01 | (-0.01, 0.00) | |
| 1245.121 | 1274 | 6 | 0.5 | 1278 | 2 | 0.2 | 0.1554 | 0.33 | ( 0.07, 1.64) | 0.33 | ( 0.07, 1.64) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.5866 |
| Male | 2023 | 19 | 0.9 | 2068 | 6 | 0.3 | 0.0088 | 0.33 | ( 0.13, 0.79) | 0.32 | ( 0.13, 0.79) | -0.01 | (-0.01, 0.00) | |
| Female | 1252 | 15 | 1.2 | 1262 | 7 | 0.6 | 0.0803 | 0.46 | ( 0.19, 1.12) | 0.46 | ( 0.19, 1.12) | -0.01 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.9461 |
| <65 | 766 | 4 | 0.5 | 705 | 1 | 0.1 | 0.2545 | 0.36 | ( 0.06, 2.27) | 0.36 | ( 0.06, 2.27) | 0.00 | (-0.01, 0.00) | |
| >=65 | 2509 | 30 | 1.2 | 2625 | 12 | 0.5 | 0.0034 | 0.38 | ( 0.20, 0.75) | 0.38 | ( 0.19, 0.74) | -0.01 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.8254 |
| North America | 434 | 9 | 2.1 | 432 | 3 | 0.7 | 0.0941 | 0.37 | ( 0.11, 1.25) | 0.36 | ( 0.11, 1.25) | -0.01 | (-0.03, 0.00) | |
| Latin America | 931 | 8 | 0.9 | 944 | 3 | 0.3 | 0.1316 | 0.37 | ( 0.10, 1.41) | 0.37 | ( 0.10, 1.41) | -0.01 | (-0.01, 0.00) | |
| Europe | 1334 | 15 | 1.1 | 1361 | 5 | 0.4 | 0.0216 | 0.33 | ( 0.12, 0.89) | 0.32 | ( 0.12, 0.89) | -0.01 | (-0.01, 0.00) | |
| Asia | 405 | 0 | 0 | 413 | 0 | 0 | 0.9949 | 0.99 | ( 0.06, 15.77) | 0.99 | ( 0.06, 15.90) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 2 | 1.2 | 180 | 2 | 1.1 | 0.9431 | 0.94 | ( 0.16, 5.34) | 0.94 | ( 0.16, 5.48) | 0.00 | (-0.03, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.3934 |
| Diabetic | 1739 | 27 | 1.6 | 1779 | 9 | 0.5 | 0.0019 | 0.32 | ( 0.15, 0.69) | 0.32 | ( 0.15, 0.68) | -0.01 | (-0.02, 0.00) | |
| Non-Diabetic | 1536 | 7 | 0.5 | 1551 | 4 | 0.3 | 0.3746 | 0.59 | ( 0.18, 1.91) | 0.59 | ( 0.18, 1.91) | 0.00 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8317 |
| <30 | 1975 | 20 | 1.0 | 1930 | 7 | 0.4 | 0.0127 | 0.35 | ( 0.15, 0.83) | 0.35 | ( 0.15, 0.83) | -0.01 | (-0.01, 0.00) | |
| >=30 | 1300 | 14 | 1.1 | 1400 | 6 | 0.4 | 0.0547 | 0.40 | ( 0.16, 1.05) | 0.40 | ( 0.15, 1.05) | -0.01 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.5422 |
| <130 | 1684 | 15 | 0.9 | 1687 | 7 | 0.4 | 0.0794 | 0.46 | ( 0.19, 1.12) | 0.45 | ( 0.18, 1.12) | 0.00 | (-0.01, 0.00) | |
| >=130 | 1591 | 19 | 1.2 | 1643 | 6 | 0.4 | 0.0074 | 0.31 | ( 0.12, 0.77) | 0.30 | ( 0.12, 0.77) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypomagnesaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.5952 |
| <75 | 1653 | 22 | 1.3 | 1612 | 8 | 0.5 | 0.0110 | 0.37 ( 0.16, 0.82) | 0.36 ( 0.16, 0.82) | -0.01 (-0.01, 0.00) | |
| 75 to <85 | 1005 | 8 | 0.8 | 1085 | 5 | 0.5 | 0.3477 | 0.60 ( 0.21, 1.75) | 0.60 ( 0.20, 1.76) | 0.00 (-0.01, 0.00) | |
| >=85 | 617 | 4 | 0.6 | 633 | 0 | 0 | 0.0942 | 0.19 ( 0.02, 1.65) | 0.19 ( 0.02, 1.65) | -0.01 (-0.01, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3464 |
| <30 | 250 | 0 | 0 | 263 | 1 | 0.4 | 0.5788 | 1.92 ( 0.19, 19.88) | 1.93 ( 0.18, 20.83) | 0.00 (-0.01, 0.02) | |
| 30 to <45 | 898 | 11 | 1.2 | 909 | 3 | 0.3 | 0.0293 | 0.27 ( 0.08, 0.96) | 0.27 ( 0.07, 0.95) | -0.01 (-0.02, 0.00) | |
| >=45 | 2126 | 23 | 1.1 | 2158 | 9 | 0.4 | 0.0102 | 0.38 ( 0.18, 0.82) | 0.38 ( 0.17, 0.82) | -0.01 (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.8060 |
| Normal (<30) | 1216 | 12 | 1.0 | 1243 | 6 | 0.5 | 0.1392 | 0.49 ( 0.18, 1.29) | 0.48 ( 0.18, 1.29) | -0.01 (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 17 | 1.1 | 1546 | 6 | 0.4 | 0.0206 | 0.35 ( 0.14, 0.89) | 0.35 ( 0.14, 0.89) | -0.01 (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 500 | 5 | 1.0 | 525 | 1 | 0.2 | 0.1188 | 0.26 ( 0.04, 1.60) | 0.26 ( 0.04, 1.60) | -0.01 (-0.02, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.4403 |
| Low, moderate or high | 2430 | 27 | 1.1 | 2495 | 12 | 0.5 | 0.0112 | 0.43 ( 0.22, 0.84) | 0.42 ( 0.21, 0.84) | -0.01 (-0.01, 0.00) | |
| Very high | 834 | 7 | 0.8 | 820 | 1 | 0.1 | 0.0485 | 0.20 ( 0.04, 1.18) | 0.20 ( 0.04, 1.17) | -0.01 (-0.01, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.2724 |
| No | 572 | 6 | 1.0 | 578 | 4 | 0.7 | 0.5427 | 0.69 ( 0.21, 2.28) | 0.69 ( 0.21, 2.30) | 0.00 (-0.01, 0.01) | |
| Yes | 2703 | 28 | 1.0 | 2752 | 9 | 0.3 | 0.0013 | 0.31 ( 0.15, 0.66) | 0.31 ( 0.15, 0.66) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.6558 |
| No | 344 | 3 | 0.9 | 349 | 0 | 0 | 0.1731 | 0.24 ( 0.03, 2.23) | 0.24 ( 0.03, 2.19) | -0.01 (-0.02, 0.00) | |
| Yes | 2931 | 31 | 1.1 | 2981 | 13 | 0.4 | 0.0050 | 0.41 ( 0.21, 0.78) | 0.41 ( 0.21, 0.78) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Metabolism and nutrition disorders
Preferred term: Hypomagnesaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | 0.5987 |
| No | 275 | 5 | 1.8 | 307 | 1 | 0.3 | 0.0967 | 0.24 ( 0.04, 1.49) | 0.24 ( 0.04, 1.48) | -0.02 | (-0.03, 0.00) | |
| Yes | 3000 | 29 | 1.0 | 3023 | 12 | 0.4 | 0.0068 | 0.41 ( 0.21, 0.80) | 0.41 ( 0.21, 0.80) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal impairment

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 286 | 8.7 | 3330 | 316 | 9.5 | 0.2935 | 1.09 ( 0.93, 1.26) | 1.09 ( 0.93, 1.29) | 0.01 (-0.01, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 171 | 5.2 | 3330 | 129 | 3.9 | 0.0082 | 0.74 | ( 0.59, 0.93) | 0.73 | ( 0.58, 0.92) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.8684 |
| 1245.110 | 2001 | 117 | 5.8 | 2052 | 90 | 4.4 | 0.0347 | 0.75 | ( 0.57, 0.98) | 0.74 | ( 0.56, 0.98) | -0.01 | (-0.03, 0.00) | |
| 1245.121 | 1274 | 54 | 4.2 | 1278 | 39 | 3.1 | 0.1097 | 0.72 | ( 0.48, 1.08) | 0.71 | ( 0.47, 1.08) | -0.01 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4217 |
| Male | 2023 | 108 | 5.3 | 2068 | 76 | 3.7 | 0.0101 | 0.69 | ( 0.52, 0.92) | 0.68 | ( 0.50, 0.91) | -0.02 | (-0.03, 0.00) | |
| Female | 1252 | 63 | 5.0 | 1262 | 53 | 4.2 | 0.3052 | 0.83 | ( 0.58, 1.19) | 0.82 | ( 0.57, 1.20) | -0.01 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3768 |
| <65 | 766 | 31 | 4.0 | 705 | 26 | 3.7 | 0.7167 | 0.91 | ( 0.55, 1.52) | 0.91 | ( 0.53, 1.54) | 0.00 | (-0.02, 0.02) | |
| >=65 | 2509 | 140 | 5.6 | 2625 | 103 | 3.9 | 0.0053 | 0.70 | ( 0.55, 0.90) | 0.69 | ( 0.53, 0.90) | -0.02 | (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | | 0.5886 |
| North America | 434 | 62 | 14.3 | 432 | 55 | 12.7 | 0.5000 | 0.89 | ( 0.64, 1.25) | 0.87 | ( 0.59, 1.29) | -0.02 | (-0.06, 0.03) | |
| Latin America | 931 | 40 | 4.3 | 944 | 30 | 3.2 | 0.2094 | 0.74 | ( 0.47, 1.18) | 0.74 | ( 0.45, 1.19) | -0.01 | (-0.03, 0.01) | |
| Europe | 1334 | 48 | 3.6 | 1361 | 29 | 2.1 | 0.0226 | 0.59 | ( 0.38, 0.93) | 0.58 | ( 0.37, 0.93) | -0.01 | (-0.03, 0.00) | |
| Asia | 405 | 10 | 2.5 | 413 | 5 | 1.2 | 0.1577 | 0.47 | ( 0.16, 1.37) | 0.47 | ( 0.16, 1.38) | -0.01 | (-0.03, 0.01) | |
| Other | 171 | 11 | 6.4 | 180 | 10 | 5.6 | 0.6768 | 0.84 | ( 0.38, 1.89) | 0.83 | ( 0.35, 1.98) | -0.01 | (-0.06, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9233 |
| Diabetic | 1739 | 105 | 6.0 | 1779 | 79 | 4.4 | 0.0314 | 0.73 | ( 0.55, 0.97) | 0.72 | ( 0.53, 0.97) | -0.02 | (-0.03, 0.00) | |
| Non-Diabetic | 1536 | 66 | 4.3 | 1551 | 50 | 3.2 | 0.1166 | 0.75 | ( 0.52, 1.08) | 0.74 | ( 0.51, 1.08) | -0.01 | (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2162 |
| <30 | 1975 | 90 | 4.6 | 1930 | 56 | 2.9 | 0.0058 | 0.63 | ( 0.46, 0.88) | 0.62 | ( 0.44, 0.87) | -0.02 | (-0.03, 0.00) | |
| >=30 | 1300 | 81 | 6.2 | 1400 | 73 | 5.2 | 0.2683 | 0.84 | ( 0.62, 1.14) | 0.83 | ( 0.60, 1.15) | -0.01 | (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7319 |
| <130 | 1684 | 97 | 5.8 | 1687 | 75 | 4.4 | 0.0763 | 0.77 | ( 0.57, 1.03) | 0.76 | ( 0.55, 1.03) | -0.01 | (-0.03, 0.00) | |
| >=130 | 1591 | 74 | 4.7 | 1643 | 54 | 3.3 | 0.0488 | 0.71 | ( 0.50, >1.00) | 0.70 | ( 0.49, 1.00) | -0.01 | (-0.03, 0.00) | |

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System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.4141 |
| <75 | 1653 | 105 | 6.4 | 1612 | 83 | 5.1 | 0.1313 | 0.81 ( 0.61, 1.07) | 0.80 ( 0.59, 1.07) | -0.01 | (-0.03, 0.00) | |
| 75 to <85 | 1005 | 42 | 4.2 | 1085 | 34 | 3.1 | 0.2055 | 0.75 ( 0.48, 1.17) | 0.74 ( 0.47, 1.18) | -0.01 | (-0.03, 0.01) | |
| >=85 | 617 | 24 | 3.9 | 633 | 12 | 1.9 | 0.0361 | 0.49 ( 0.25, 0.97) | 0.48 ( 0.24, 0.97) | -0.02 | (-0.04, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.0774 |
| <30 | 250 | 22 | 8.8 | 263 | 29 | 11.0 | 0.3281 | 1.31 ( 0.76, 2.24) | 1.34 ( 0.74, 2.43) | 0.03 | (-0.03, 0.08) | |
| 30 to <45 | 898 | 62 | 6.9 | 909 | 42 | 4.6 | 0.0357 | 0.67 ( 0.46, 0.98) | 0.65 ( 0.43, 0.97) | -0.02 | (-0.04, 0.00) | |
| >=45 | 2126 | 87 | 4.1 | 2158 | 58 | 2.7 | 0.0103 | 0.65 ( 0.47, 0.91) | 0.64 ( 0.46, 0.90) | -0.01 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.3386 |
| Normal (<30) | 1216 | 53 | 4.4 | 1243 | 45 | 3.6 | 0.3478 | 0.83 ( 0.56, 1.23) | 0.82 ( 0.55, 1.24) | -0.01 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 88 | 5.7 | 1546 | 56 | 3.6 | 0.0058 | 0.63 ( 0.46, 0.88) | 0.62 ( 0.44, 0.87) | -0.02 | (-0.04,-0.01) | |
| Macroalbuminuria (>300) | 500 | 28 | 5.6 | 525 | 28 | 5.3 | 0.8682 | 0.96 ( 0.57, 1.60) | 0.96 ( 0.56, 1.64) | 0.00 | (-0.03, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.3616 |
| Low, moderate or high | 2430 | 102 | 4.2 | 2495 | 73 | 2.9 | 0.0149 | 0.69 ( 0.52, 0.93) | 0.69 ( 0.50, 0.93) | -0.01 | (-0.02, 0.00) | |
| Very high | 834 | 67 | 8.0 | 820 | 56 | 6.8 | 0.3744 | 0.86 ( 0.61, 1.21) | 0.85 ( 0.58, 1.22) | -0.01 | (-0.04, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.5868 |
| No | 572 | 32 | 5.6 | 578 | 27 | 4.7 | 0.4905 | 0.84 ( 0.51, 1.38) | 0.83 ( 0.49, 1.41) | -0.01 | (-0.03, 0.02) | |
| Yes | 2703 | 139 | 5.1 | 2752 | 102 | 3.7 | 0.0094 | 0.72 ( 0.56, 0.92) | 0.71 ( 0.55, 0.92) | -0.01 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.4340 |
| No | 344 | 25 | 7.3 | 349 | 15 | 4.3 | 0.0880 | 0.59 ( 0.32, 1.09) | 0.57 ( 0.29, 1.10) | -0.03 | (-0.07, 0.00) | |
| Yes | 2931 | 146 | 5.0 | 2981 | 114 | 3.8 | 0.0279 | 0.77 ( 0.60, 0.97) | 0.76 ( 0.59, 0.97) | -0.01 | (-0.02, 0.00) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | 0.2146 |
| No | 275 | 13 | 4.7 | 307 | 6 | 2.0 | 0.0613 | 0.41 ( 0.16, 1.08) | 0.40 ( 0.15, 1.07) | -0.03 | (-0.06, 0.00) | |
| Yes | 3000 | 158 | 5.3 | 3023 | 123 | 4.1 | 0.0263 | 0.77 ( 0.61, 0.97) | 0.76 ( 0.60, 0.97) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 134 | 4.1 | 3330 | 110 | 3.3 | 0.0876 | 0.81 ( 0.63, 1.03) | 0.80 ( 0.62, 1.03) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Chronic kidney disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 103 | 3.1 | 3330 | 92 | 2.8 | 0.3455 | 0.88 ( 0.66, 1.15) | 0.87 ( 0.66, 1.16) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Microalbuminuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 39 | 1.2 | 3330 | 45 | 1.4 | 0.5682 | 1.13 ( 0.74, 1.73) | 1.13 ( 0.74, 1.75) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

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System organ class: Renal and urinary disorders
Preferred term: Haematuria

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 40 | 1.2 | 3330 | 34 | 1.0 | 0.4388 | 0.84 ( 0.53, 1.32) | 0.83 ( 0.53, 1.32) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Diarrhoea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 138 | 4.2 | 3330 | 147 | 4.4 | 0.6985 | 1.05 ( 0.83, 1.31) | 1.05 ( 0.83, 1.33) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Constipation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 93 | 2.8 | 3330 | 130 | 3.9 | 0.0171 | 1.37 | ( 1.06, 1.78) | 1.39 | ( 1.06, 1.82) | 0.01 | ( 0.00, 0.02) | |
| Study | | | | | | | | | | | | | | 0.2771 |
| 1245.110 | 2001 | 66 | 3.3 | 2052 | 84 | 4.1 | 0.1801 | 1.24 | ( 0.90, 1.70) | 1.25 | ( 0.90, 1.74) | 0.01 | ( 0.00, 0.02) | |
| 1245.121 | 1274 | 27 | 2.1 | 1278 | 46 | 3.6 | 0.0249 | 1.70 | ( 1.06, 2.71) | 1.72 | ( 1.07, 2.79) | 0.01 | ( 0.00, 0.03) | |
| Sex | | | | | | | | | | | | | | 0.3920 |
| Male | 2023 | 60 | 3.0 | 2068 | 77 | 3.7 | 0.1792 | 1.25 | ( 0.90, 1.75) | 1.26 | ( 0.90, 1.78) | 0.01 | ( 0.00, 0.02) | |
| Female | 1252 | 33 | 2.6 | 1262 | 53 | 4.2 | 0.0319 | 1.59 | ( 1.04, 2.44) | 1.61 | ( 1.04, 2.51) | 0.02 | ( 0.00, 0.03) | |
| Age [years] | | | | | | | | | | | | | | 0.2617 |
| <65 | 766 | 18 | 2.3 | 705 | 16 | 2.3 | 0.9048 | 0.96 | ( 0.49, 1.87) | 0.96 | ( 0.49, 1.90) | 0.00 | (-0.02, 0.01) | |
| >=65 | 2509 | 75 | 3.0 | 2625 | 114 | 4.3 | 0.0100 | 1.45 | ( 1.09, 1.94) | 1.47 | ( 1.10, 1.98) | 0.01 | ( 0.00, 0.02) | |
| Region | | | | | | | | | | | | | | 0.6299 |
| North America | 434 | 22 | 5.1 | 432 | 26 | 6.0 | 0.5454 | 1.18 | ( 0.68, 2.05) | 1.20 | ( 0.67, 2.15) | 0.01 | (-0.02, 0.04) | |
| Latin America | 931 | 11 | 1.2 | 944 | 17 | 1.8 | 0.2594 | 1.54 | ( 0.72, 3.27) | 1.55 | ( 0.72, 3.33) | 0.01 | ( 0.00, 0.02) | |
| Europe | 1334 | 19 | 1.4 | 1361 | 21 | 1.5 | 0.8010 | 1.08 | ( 0.58, 2.01) | 1.08 | ( 0.58, 2.03) | 0.00 | (-0.01, 0.01) | |
| Asia | 405 | 31 | 7.7 | 413 | 55 | 13.3 | 0.0083 | 1.74 | ( 1.14, 2.63) | 1.85 | ( 1.16, 2.93) | 0.06 | ( 0.01, 0.10) | |
| Other | 171 | 10 | 5.8 | 180 | 11 | 6.1 | 0.9286 | 1.04 | ( 0.45, 2.39) | 1.04 | ( 0.43, 2.52) | 0.00 | (-0.05, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.5250 |
| Diabetic | 1739 | 48 | 2.8 | 1779 | 73 | 4.1 | 0.0292 | 1.49 | ( 1.04, 2.12) | 1.51 | ( 1.04, 2.18) | 0.01 | ( 0.00, 0.03) | |
| Non-Diabetic | 1536 | 45 | 2.9 | 1551 | 57 | 3.7 | 0.2495 | 1.25 | ( 0.85, 1.84) | 1.26 | ( 0.85, 1.88) | 0.01 | (-0.01, 0.02) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.1671 |
| <30 | 1975 | 58 | 2.9 | 1930 | 90 | 4.7 | 0.0051 | 1.58 | ( 1.14, 2.19) | 1.61 | ( 1.15, 2.25) | 0.02 | ( 0.01, 0.03) | |
| >=30 | 1300 | 35 | 2.7 | 1400 | 40 | 2.9 | 0.7615 | 1.07 | ( 0.69, 1.68) | 1.07 | ( 0.68, 1.70) | 0.00 | (-0.01, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6072 |
| <130 | 1684 | 46 | 2.7 | 1687 | 68 | 4.0 | 0.0397 | 1.47 | ( 1.02, 2.12) | 1.49 | ( 1.02, 2.18) | 0.01 | ( 0.00, 0.02) | |
| >=130 | 1591 | 47 | 3.0 | 1643 | 62 | 3.8 | 0.1954 | 1.28 | ( 0.88, 1.86) | 1.29 | ( 0.88, 1.90) | 0.01 | ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Constipation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.1921 |
| <75 | 1653 | 51 | 3.1 | 1612 | 81 | 5.0 | 0.0054 | 1.62 ( 1.15, | 2.28) | 1.65 ( 1.16, | 2.36) | 0.02 ( 0.01, 0.03) | |
| 75 to <85 | 1005 | 22 | 2.2 | 1085 | 32 | 2.9 | 0.2717 | 1.35 ( 0.79, | 2.30) | 1.36 ( 0.78, | 2.35) | 0.01 (-0.01, 0.02) | |
| >=85 | 617 | 20 | 3.2 | 633 | 17 | 2.7 | 0.5617 | 0.83 ( 0.44, | 1.57) | 0.82 ( 0.43, | 1.59) | -0.01 (-0.02, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.0097 |
| <30 | 250 | 9 | 3.6 | 263 | 17 | 6.5 | 0.1448 | 1.81 ( 0.80, | 4.06) | 1.86 ( 0.81, | 4.29) | 0.03 (-0.01, 0.07) | |
| 30 to <45 | 898 | 40 | 4.5 | 909 | 31 | 3.4 | 0.2422 | 0.76 ( 0.48, | 1.20) | 0.75 ( 0.47, | 1.21) | -0.01 (-0.03, 0.01) | |
| >=45 | 2126 | 44 | 2.1 | 2158 | 82 | 3.8 | 0.0008 | 1.83 ( 1.28, | 2.63) | 1.87 ( 1.29, | 2.71) | 0.02 ( 0.01, 0.03) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.1395 |
| Normal (<30) | 1216 | 27 | 2.2 | 1243 | 42 | 3.4 | 0.0828 | 1.52 ( 0.94, | 2.45) | 1.54 ( 0.94, | 2.51) | 0.01 ( 0.00, 0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 45 | 2.9 | 1546 | 71 | 4.6 | 0.0144 | 1.57 ( 1.09, | 2.27) | 1.60 ( 1.09, | 2.34) | 0.02 ( 0.00, 0.03) | |
| Macroalbuminuria (>300) | 500 | 21 | 4.2 | 525 | 17 | 3.2 | 0.4178 | 0.77 ( 0.41, | 1.45) | 0.76 ( 0.40, | 1.47) | -0.01 (-0.03, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.2872 |
| Low, moderate or high | 2430 | 57 | 2.3 | 2495 | 90 | 3.6 | 0.0096 | 1.53 ( 1.11, | 2.13) | 1.55 ( 1.11, | 2.18) | 0.01 ( 0.00, 0.02) | |
| Very high | 834 | 36 | 4.3 | 820 | 40 | 4.9 | 0.5620 | 1.14 ( 0.73, | 1.77) | 1.15 ( 0.72, | 1.82) | 0.01 (-0.01, 0.03) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.6986 |
| No | 572 | 31 | 5.4 | 578 | 40 | 6.9 | 0.2964 | 1.27 ( 0.81, | 2.01) | 1.29 ( 0.80, | 2.10) | 0.01 (-0.01, 0.04) | |
| Yes | 2703 | 62 | 2.3 | 2752 | 90 | 3.3 | 0.0299 | 1.42 ( 1.03, | 1.95) | 1.44 ( 1.03, | 1.99) | 0.01 ( 0.00, 0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.1724 |
| No | 344 | 14 | 4.1 | 349 | 12 | 3.4 | 0.6382 | 0.83 ( 0.39, | 1.78) | 0.83 ( 0.38, | 1.82) | -0.01 (-0.04, 0.02) | |
| Yes | 2931 | 79 | 2.7 | 2981 | 118 | 4.0 | 0.0072 | 1.46 ( 1.11, | 1.94) | 1.48 ( 1.11, | 1.98) | 0.01 ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Constipation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.0303 |
| No | 275 | 14 | 5.1 | 307 | 9 | 2.9 | 0.1913 | 0.58 ( 0.26, 1.32) | 0.57 ( 0.24, 1.34) | -0.02 (-0.05, 0.01) | |
| Yes | 3000 | 79 | 2.6 | 3023 | 121 | 4.0 | 0.0031 | 1.52 ( 1.15, 2.01) | 1.54 ( 1.15, 2.05) | 0.01 ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Nausea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 59 | 1.8 | 3330 | 79 | 2.4 | 0.1065 | 1.32 ( 0.94, 1.84) | 1.32 ( 0.94, 1.86) | 0.01 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Vomiting

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 52 | 1.6 | 3330 | 40 | 1.2 | 0.1765 | 0.75 ( 0.50, 1.14) | 0.75 ( 0.50, 1.14) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Abdominal pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 31 | 0.9 | 3330 | 43 | 1.3 | 0.1818 | 1.37 ( 0.86, 2.16) | 1.37 ( 0.86, 2.18) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Gastritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 40 | 1.2 | 3330 | 35 | 1.1 | 0.5027 | 0.86 ( 0.55, 1.35) | 0.86 ( 0.54, 1.35) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Abdominal pain upper

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 34 | 1.0 | 3330 | 39 | 1.2 | 0.6090 | 1.13 ( 0.71, 1.78) | 1.13 ( 0.71, 1.79) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Gastrointestinal disorders
Preferred term: Dyspepsia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 36 | 1.1 | 3330 | 35 | 1.1 | 0.8469 | 0.96 ( 0.60, 1.52) | 0.95 ( 0.60, 1.52) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 251 | 7.7 | 3330 | 294 | 8.8 | 0.0853 | 1.15 ( 0.98, 1.35) | 1.17 ( 0.98, 1.39) | 0.01 ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypertension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 204 | 6.2 | 3330 | 217 | 6.5 | 0.6716 | 1.04 ( 0.87, 1.25) | 1.04 ( 0.86, 1.27) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Peripheral arterial occlusive disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 44 | 1.3 | 3330 | 42 | 1.3 | 0.7606 | 0.94 ( 0.62, 1.43) | 0.94 ( 0.61, 1.43) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Dizziness

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 115 | 3.5 | 3330 | 139 | 4.2 | 0.1643 | 1.19 ( 0.93, 1.51) | 1.20 ( 0.93, 1.54) | 0.01 ( 0.00, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Syncope

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 64 | 2.0 | 3330 | 75 | 2.3 | 0.4049 | 1.15 ( 0.83, 1.60) | 1.15 ( 0.82, 1.62) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Headache

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 64 | 2.0 | 3330 | 68 | 2.0 | 0.8120 | 1.04 ( 0.74, 1.46) | 1.04 ( 0.74, 1.47) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 47 | 1.4 | 3330 | 49 | 1.5 | 0.9126 | 1.02 ( 0.69, 1.52) | 1.02 ( 0.68, 1.53) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Arthralgia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 105 | 3.2 | 3330 | 126 | 3.8 | 0.2086 | 1.18 ( 0.91, 1.52) | 1.18 ( 0.91, 1.54) | 0.01 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Back pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 121 | 3.7 | 3330 | 114 | 3.4 | 0.5379 | 0.92 ( 0.72, 1.19) | 0.92 ( 0.71, 1.20) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Pain in extremity

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Overall | 3275 | 84 | 2.6 | 3330 | 61 | 1.8 | 0.0397 | 0.71 ( 0.51, | 0.99) | 0.71 ( 0.51, | 0.99) | -0.01 (-0.01, | 0.00) | |
| Study | | | | | | | | | | | | | | 0.1900 |
| 1245.110 | 2001 | 68 | 3.4 | 2052 | 44 | 2.1 | 0.0149 | 0.63 ( 0.43, | 0.92) | 0.62 ( 0.42, | 0.91) | -0.01 (-0.02, | 0.00) | |
| 1245.121 | 1274 | 16 | 1.3 | 1278 | 17 | 1.3 | 0.8681 | 1.06 ( 0.54, | 2.09) | 1.06 ( 0.53, | 2.11) | 0.00 (-0.01, | 0.01) | |
| Sex | | | | | | | | | | | | | | 0.7921 |
| Male | 2023 | 42 | 2.1 | 2068 | 32 | 1.5 | 0.2016 | 0.74 ( 0.47, | 1.17) | 0.74 ( 0.46, | 1.18) | -0.01 (-0.01, | 0.00) | |
| Female | 1252 | 42 | 3.4 | 1262 | 29 | 2.3 | 0.1050 | 0.68 ( 0.43, | 1.09) | 0.67 ( 0.42, | 1.09) | -0.01 (-0.02, | 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.7007 |
| <65 | 766 | 22 | 2.9 | 705 | 13 | 1.8 | 0.1880 | 0.64 ( 0.32, | 1.25) | 0.63 ( 0.31, | 1.26) | -0.01 (-0.03, | 0.00) | |
| >=65 | 2509 | 62 | 2.5 | 2625 | 48 | 1.8 | 0.1143 | 0.74 ( 0.51, | 1.08) | 0.74 ( 0.50, | 1.08) | -0.01 (-0.01, | 0.00) | |
| Region | | | | | | | | | | | | | | 0.4412 |
| North America | 434 | 30 | 6.9 | 432 | 17 | 3.9 | 0.0527 | 0.57 ( 0.32, | 1.02) | 0.55 ( 0.30, | 1.01) | -0.03 (-0.06, | 0.00) | |
| Latin America | 931 | 16 | 1.7 | 944 | 19 | 2.0 | 0.6043 | 1.19 ( 0.62, | 2.30) | 1.19 ( 0.61, | 2.34) | 0.00 (-0.01, | 0.02) | |
| Europe | 1334 | 18 | 1.3 | 1361 | 13 | 1.0 | 0.3310 | 0.71 ( 0.35, | 1.43) | 0.70 ( 0.34, | 1.44) | 0.00 (-0.01, | 0.00) | |
| Asia | 405 | 14 | 3.5 | 413 | 7 | 1.7 | 0.0935 | 0.47 ( 0.19, | 1.16) | 0.46 ( 0.18, | 1.16) | -0.02 (-0.04, | 0.00) | |
| Other | 171 | 6 | 3.5 | 180 | 5 | 2.8 | 0.6943 | 0.79 ( 0.25, | 2.52) | 0.79 ( 0.24, | 2.61) | -0.01 (-0.04, | 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.8993 |
| Diabetic | 1739 | 46 | 2.6 | 1779 | 33 | 1.9 | 0.1081 | 0.70 ( 0.45, | 1.09) | 0.69 ( 0.44, | 1.09) | -0.01 (-0.02, | 0.00) | |
| Non-Diabetic | 1536 | 38 | 2.5 | 1551 | 28 | 1.8 | 0.1959 | 0.73 ( 0.45, | 1.18) | 0.72 ( 0.44, | 1.18) | -0.01 (-0.02, | 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.7312 |
| <30 | 1975 | 48 | 2.4 | 1930 | 32 | 1.7 | 0.0789 | 0.67 ( 0.43, | 1.05) | 0.67 ( 0.43, | 1.05) | -0.01 (-0.02, | 0.00) | |
| >=30 | 1300 | 36 | 2.8 | 1400 | 29 | 2.1 | 0.2579 | 0.76 ( 0.47, | 1.23) | 0.75 ( 0.46, | 1.23) | -0.01 (-0.02, | 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.8273 |
| <130 | 1684 | 36 | 2.1 | 1687 | 27 | 1.6 | 0.2332 | 0.74 ( 0.45, | 1.22) | 0.74 ( 0.44, | 1.22) | -0.01 (-0.01, | 0.00) | |
| >=130 | 1591 | 48 | 3.0 | 1643 | 34 | 2.1 | 0.0906 | 0.69 ( 0.45, | 1.06) | 0.68 ( 0.44, | 1.06) | -0.01 (-0.02, | 0.00) | |

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A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Pain in extremity

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.0544 |
| <75 | 1653 | 43 | 2.6 | 1612 | 37 | 2.3 | 0.5430 | 0.87 ( 0.57, | 1.35) | 0.87 ( 0.56, | 1.36) | 0.00 (-0.01, 0.01) | |
| 75 to <85 | 1005 | 19 | 1.9 | 1085 | 18 | 1.7 | 0.6975 | 0.88 ( 0.46, | 1.67) | 0.88 ( 0.46, | 1.69) | 0.00 (-0.01, 0.01) | |
| >=85 | 617 | 22 | 3.6 | 633 | 6 | 0.9 | 0.0018 | 0.27 ( 0.11, | 0.65) | 0.26 ( 0.10, | 0.64) | -0.03 (-0.04,-0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.9107 |
| <30 | 250 | 6 | 2.4 | 263 | 4 | 1.5 | 0.5392 | 0.68 ( 0.19, | 2.38) | 0.67 ( 0.19, | 2.42) | -0.01 (-0.03, 0.02) | |
| 30 to <45 | 898 | 26 | 2.9 | 909 | 17 | 1.9 | 0.1469 | 0.64 ( 0.35, | 1.17) | 0.63 ( 0.34, | 1.18) | -0.01 (-0.02, 0.00) | |
| >=45 | 2126 | 52 | 2.4 | 2158 | 40 | 1.9 | 0.1668 | 0.75 ( 0.50, | 1.13) | 0.75 ( 0.49, | 1.13) | -0.01 (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.6661 |
| Normal (<30) | 1216 | 29 | 2.4 | 1243 | 25 | 2.0 | 0.5175 | 0.84 ( 0.50, | 1.42) | 0.84 ( 0.49, | 1.44) | 0.00 (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 35 | 2.3 | 1546 | 23 | 1.5 | 0.1067 | 0.65 ( 0.39, | 1.10) | 0.65 ( 0.38, | 1.10) | -0.01 (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 500 | 20 | 4.0 | 525 | 12 | 2.3 | 0.1209 | 0.58 ( 0.29, | 1.17) | 0.57 ( 0.27, | 1.17) | -0.02 (-0.04, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.8739 |
| Low, moderate or high | 2430 | 61 | 2.5 | 2495 | 45 | 1.8 | 0.0793 | 0.71 ( 0.49, | 1.04) | 0.71 ( 0.48, | 1.04) | -0.01 (-0.02, 0.00) | |
| Very high | 834 | 23 | 2.8 | 820 | 15 | 1.8 | 0.2208 | 0.67 ( 0.35, | 1.28) | 0.66 ( 0.34, | 1.28) | -0.01 (-0.02, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.3784 |
| No | 572 | 22 | 3.8 | 578 | 12 | 2.1 | 0.0788 | 0.54 ( 0.27, | 1.09) | 0.53 ( 0.26, | 1.09) | -0.02 (-0.04, 0.00) | |
| Yes | 2703 | 62 | 2.3 | 2752 | 49 | 1.8 | 0.1694 | 0.77 ( 0.53, | 1.12) | 0.77 ( 0.53, | 1.12) | -0.01 (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.3317 |
| No | 344 | 10 | 2.9 | 349 | 4 | 1.1 | 0.1157 | 0.43 ( 0.14, | 1.27) | 0.42 ( 0.14, | 1.28) | -0.02 (-0.04, 0.00) | |
| Yes | 2931 | 74 | 2.5 | 2981 | 57 | 1.9 | 0.1016 | 0.75 ( 0.54, | 1.06) | 0.75 ( 0.53, | 1.06) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Pain in extremity

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.4866 |
| No | 275 | 6 | 2.2 | 307 | 3 | 1.0 | 0.2368 | 0.44 ( 0.11, 1.77) | 0.44 ( 0.11, 1.78) | -0.01 (-0.03, 0.01) | |
| Yes | 3000 | 78 | 2.6 | 3023 | 58 | 1.9 | 0.0709 | 0.74 ( 0.53, 1.03) | 0.73 ( 0.52, 1.03) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Osteoarthritis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 79 | 2.4 | 3330 | 72 | 2.2 | 0.4822 | 0.89 ( 0.65, 1.22) | 0.89 ( 0.64, 1.23) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Musculoskeletal and connective tissue disorders
Preferred term: Muscle spasms

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 44 | 1.3 | 3330 | 34 | 1.0 | 0.2175 | 0.76 ( 0.48, 1.18) | 0.75 ( 0.48, 1.18) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Dyspnoea

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 110 | 3.4 | 3330 | 102 | 3.1 | 0.4876 | 0.91 ( 0.70, 1.19) | 0.91 ( 0.69, 1.19) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Chronic obstructive pulmonary disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 98 | 3.0 | 3330 | 76 | 2.3 | 0.0672 | 0.76 ( 0.57, 1.02) | 0.75 ( 0.56, 1.02) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Cough

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 76 | 2.3 | 3330 | 89 | 2.7 | 0.3551 | 1.15 ( 0.85, 1.56) | 1.16 ( 0.85, 1.58) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Epistaxis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 57 | 1.7 | 3330 | 50 | 1.5 | 0.4305 | 0.86 ( 0.59, 1.25) | 0.86 ( 0.58, 1.26) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Pleural effusion

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 28 | 0.9 | 3330 | 34 | 1.0 | 0.4902 | 1.19 ( 0.72, 1.96) | 1.19 ( 0.72, 1.97) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Oedema peripheral

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 100 | 3.1 | 3330 | 97 | 2.9 | 0.7206 | 0.95 ( 0.72, 1.25) | 0.95 ( 0.71, 1.26) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 85 | 2.6 | 3330 | 94 | 2.8 | 0.5773 | 1.09 ( 0.81, 1.45) | 1.09 ( 0.81, 1.47) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Fatigue

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 60 | 1.8 | 3330 | 73 | 2.2 | 0.2955 | 1.20 ( 0.85, 1.68) | 1.20 ( 0.85, 1.70) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Non-cardiac chest pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 59 | 1.8 | 3330 | 63 | 1.9 | 0.7937 | 1.05 ( 0.74, 1.49) | 1.05 ( 0.73, 1.50) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Asthenia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 39 | 1.2 | 3330 | 37 | 1.1 | 0.7571 | 0.93 ( 0.60, 1.46) | 0.93 ( 0.59, 1.46) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Chest pain

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 33 | 1.0 | 3330 | 37 | 1.1 | 0.6920 | 1.10 ( 0.69, 1.75) | 1.10 ( 0.69, 1.76) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 222 | 6.8 | 3330 | 240 | 7.2 | 0.5280 | 1.06 ( 0.89, 1.26) | 1.06 ( 0.88, 1.29) | 0.00 (-0.01, 0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Contusion

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 63 | 1.9 | 3330 | 73 | 2.2 | 0.4536 | 1.14 ( 0.81, 1.58) | 1.14 ( 0.81, 1.60) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Skin laceration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 22 | 0.7 | 3330 | 45 | 1.4 | 0.0060 | 2.01 ( 1.21, 3.33) | | 2.02 ( 1.21, 3.37) | | 0.01 ( 0.00, 0.01) | |
| Study | | | | | | | | | | | | | 0.2516 |
| 1245.110 | 2001 | 18 | 0.9 | 2052 | 31 | 1.5 | 0.0751 | 1.68 ( 0.94, 2.99) | | 1.69 ( 0.94, 3.03) | | 0.01 ( 0.00, 0.01) | |
| 1245.121 | 1274 | 4 | 0.3 | 1278 | 14 | 1.1 | 0.0184 | 3.49 ( 1.15, 10.57) | | 3.52 ( 1.15, 10.71) | | 0.01 ( 0.00, 0.01) | |
| Sex | | | | | | | | | | | | | 0.4104 |
| Male | 2023 | 13 | 0.6 | 2068 | 31 | 1.5 | 0.0080 | 2.33 ( 1.22, 4.44) | | 2.35 ( 1.23, 4.51) | | 0.01 ( 0.00, 0.01) | |
| Female | 1252 | 9 | 0.7 | 1262 | 14 | 1.1 | 0.3176 | 1.51 ( 0.67, 3.39) | | 1.51 ( 0.67, 3.44) | | 0.00 ( 0.00, 0.01) | |
| Age [years] | | | | | | | | | | | | | 0.9928 |
| <65 | 766 | 2 | 0.3 | 705 | 4 | 0.6 | 0.3852 | 1.95 ( 0.42, 9.02) | | 1.95 ( 0.42, 9.13) | | 0.00 ( 0.00, 0.01) | |
| >=65 | 2509 | 20 | 0.8 | 2625 | 41 | 1.6 | 0.0113 | 1.96 ( 1.15, 3.34) | | 1.98 ( 1.16, 3.39) | | 0.01 ( 0.00, 0.01) | |
| Region | | | | | | | | | | | | | 0.6836 |
| North America | 434 | 9 | 2.1 | 432 | 25 | 5.8 | 0.0050 | 2.79 ( 1.32, 5.90) | | 2.89 ( 1.33, 6.27) | | 0.04 ( 0.01, 0.06) | |
| Latin America | 931 | 0 | 0 | 944 | 0 | 0 | 0.9908 | 0.98 ( 0.06, 15.70) | | 0.98 ( 0.06, 15.75) | | 0.00 ( 0.00, 0.00) | |
| Europe | 1334 | 5 | 0.4 | 1361 | 7 | 0.5 | 0.5946 | 1.36 ( 0.43, 4.29) | | 1.37 ( 0.43, 4.32) | | 0.00 ( 0.00, 0.01) | |
| Asia | 405 | 2 | 0.5 | 413 | 5 | 1.2 | 0.2651 | 2.46 ( 0.48, 12.67) | | 2.48 ( 0.48, 12.89) | | 0.01 (-0.01, 0.02) | |
| Other | 171 | 6 | 3.5 | 180 | 8 | 4.4 | 0.6833 | 1.24 ( 0.44, 3.50) | | 1.25 ( 0.42, 3.70) | | 0.01 (-0.03, 0.05) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.1377 |
| Diabetic | 1739 | 6 | 0.3 | 1779 | 21 | 1.2 | 0.0046 | 3.41 ( 1.38, 8.42) | | 3.44 ( 1.39, 8.54) | | 0.01 ( 0.00, 0.01) | |
| Non-Diabetic | 1536 | 16 | 1.0 | 1551 | 24 | 1.5 | 0.2167 | 1.48 ( 0.79, 2.78) | | 1.49 ( 0.79, 2.82) | | 0.01 ( 0.00, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.9477 |
| <30 | 1975 | 12 | 0.6 | 1930 | 23 | 1.2 | 0.0553 | 1.95 ( 0.97, 3.90) | | 1.96 ( 0.97, 3.95) | | 0.01 ( 0.00, 0.01) | |
| >=30 | 1300 | 10 | 0.8 | 1400 | 22 | 1.6 | 0.0556 | 2.01 ( 0.97, 4.19) | | 2.03 ( 0.97, 4.25) | | 0.01 ( 0.00, 0.02) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.3256 |
| <130 | 1684 | 11 | 0.7 | 1687 | 28 | 1.7 | 0.0068 | 2.52 ( 1.26, 5.03) | | 2.54 ( 1.26, 5.13) | | 0.01 ( 0.00, 0.02) | |
| >=130 | 1591 | 11 | 0.7 | 1643 | 17 | 1.0 | 0.2859 | 1.50 ( 0.71, 3.20) | | 1.51 ( 0.70, 3.24) | | 0.00 ( 0.00, 0.01) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Skin laceration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | 0.1358 |
| <75 | 1653 | 13 | 0.8 | 1612 | 36 | 2.2 | 0.0007 | 2.81 ( 1.50, 5.27) | 2.86 ( 1.51, 5.40) | 0.01 ( 0.01, 0.02) | |
| 75 to <85 | 1005 | 7 | 0.7 | 1085 | 6 | 0.6 | 0.6833 | 0.80 ( 0.27, 2.37) | 0.80 ( 0.27, 2.38) | 0.00 (-0.01, 0.01) | |
| >=85 | 617 | 2 | 0.3 | 633 | 3 | 0.5 | 0.6767 | 1.46 ( 0.25, 8.68) | 1.46 ( 0.24, 8.76) | 0.00 (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | 0.3702 |
| <30 | 250 | 2 | 0.8 | 263 | 6 | 2.3 | 0.1926 | 2.41 ( 0.61, 9.54) | 2.43 ( 0.59, 10.13) | 0.02 (-0.01, 0.04) | |
| 30 to <45 | 898 | 12 | 1.3 | 909 | 16 | 1.8 | 0.4731 | 1.31 ( 0.62, 2.75) | 1.32 ( 0.62, 2.80) | 0.00 (-0.01, 0.02) | |
| >=45 | 2126 | 8 | 0.4 | 2158 | 23 | 1.1 | 0.0083 | 2.80 ( 1.26, 6.24) | 2.82 ( 1.26, 6.32) | 0.01 ( 0.00, 0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | 0.5639 |
| Normal (<30) | 1216 | 8 | 0.7 | 1243 | 14 | 1.1 | 0.2193 | 1.71 ( 0.72, 4.05) | 1.72 ( 0.72, 4.10) | 0.00 ( 0.00, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 13 | 0.8 | 1546 | 24 | 1.6 | 0.0706 | 1.84 ( 0.94, 3.59) | 1.85 ( 0.94, 3.65) | 0.01 ( 0.00, 0.01) | |
| Macroalbuminuria (>300) | 500 | 1 | 0.2 | 525 | 7 | 1.3 | 0.0509 | 4.80 ( 0.84, 27.48) | 4.86 ( 0.84, 28.11) | 0.01 ( 0.00, 0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | 0.8255 |
| Low, moderate or high | 2430 | 14 | 0.6 | 2495 | 28 | 1.1 | 0.0395 | 1.93 ( 1.02, 3.65) | 1.94 ( 1.02, 3.69) | 0.01 ( 0.00, 0.01) | |
| Very high | 834 | 8 | 1.0 | 820 | 17 | 2.1 | 0.0616 | 2.17 ( 0.94, 4.99) | 2.20 ( 0.94, 5.11) | 0.01 ( 0.00, 0.02) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | 0.6874 |
| No | 572 | 9 | 1.6 | 578 | 16 | 2.8 | 0.1663 | 1.76 ( 0.78, 3.95) | 1.78 ( 0.78, 4.06) | 0.01 ( 0.00, 0.03) | |
| Yes | 2703 | 13 | 0.5 | 2752 | 29 | 1.1 | 0.0163 | 2.18 ( 1.14, 4.17) | 2.19 ( 1.14, 4.22) | 0.01 ( 0.00, 0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | 0.7101 |
| No | 344 | 3 | 0.9 | 349 | 5 | 1.4 | 0.5029 | 1.57 ( 0.42, 5.92) | 1.58 ( 0.41, 6.07) | 0.01 (-0.01, 0.02) | |
| Yes | 2931 | 19 | 0.6 | 2981 | 40 | 1.3 | 0.0076 | 2.06 ( 1.20, 3.55) | 2.08 ( 1.20, 3.59) | 0.01 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Skin laceration

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.9611 |
| No | 275 | 1 | 0.4 | 307 | 3 | 1.0 | 0.4398 | 2.08 ( 0.31, 13.82) | 2.09 ( 0.31, 14.17) | 0.01 (-0.01, 0.02) | |
| Yes | 3000 | 21 | 0.7 | 3023 | 42 | 1.4 | 0.0088 | 1.98 ( 1.18, 3.33) | 1.99 ( 1.18, 3.37) | 0.01 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Limb injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 37 | 1.1 | 3330 | 38 | 1.1 | 0.9703 | 1.01 ( 0.64, 1.58) | 1.01 ( 0.64, 1.59) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Glomerular filtration rate decreased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 46 | 1.4 | 3330 | 32 | 1.0 | 0.0947 | 0.68 ( 0.44, 1.07) | 0.68 ( 0.43, 1.07) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Weight decreased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 34 | 1.0 | 3330 | 38 | 1.1 | 0.6945 | 1.10 ( 0.69, 1.74) | 1.10 ( 0.69, 1.75) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Investigations
Preferred term: Gamma-glutamyltransferase increased

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 33 | 1.0 | 3330 | 21 | 0.6 | 0.0890 | 0.63 ( 0.36, 1.08) | 0.62 ( 0.36, 1.08) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 229 | 7.0 | 3330 | 171 | 5.1 | 0.0013 | 0.73 | ( 0.60, 0.89) | 0.72 | ( 0.58, 0.88) | -0.02 | (-0.03,-0.01) | |
| Study | | | | | | | | | | | | | | 0.6898 |
| 1245.110 | 2001 | 172 | 8.6 | 2052 | 132 | 6.4 | 0.0090 | 0.75 | ( 0.60, 0.93) | 0.73 | ( 0.58, 0.93) | -0.02 | (-0.04,-0.01) | |
| 1245.121 | 1274 | 57 | 4.5 | 1278 | 39 | 3.1 | 0.0590 | 0.68 | ( 0.46, 1.02) | 0.67 | ( 0.44, 1.02) | -0.01 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.6809 |
| Male | 2023 | 137 | 6.8 | 2068 | 106 | 5.1 | 0.0246 | 0.76 | ( 0.59, 0.97) | 0.74 | ( 0.57, 0.96) | -0.02 | (-0.03, 0.00) | |
| Female | 1252 | 92 | 7.3 | 1262 | 65 | 5.2 | 0.0202 | 0.70 | ( 0.51, 0.95) | 0.68 | ( 0.49, 0.94) | -0.02 | (-0.04, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.6381 |
| <65 | 766 | 47 | 6.1 | 705 | 35 | 5.0 | 0.3080 | 0.80 | ( 0.52, 1.23) | 0.79 | ( 0.50, 1.24) | -0.01 | (-0.04, 0.01) | |
| >=65 | 2509 | 182 | 7.3 | 2625 | 136 | 5.2 | 0.0021 | 0.72 | ( 0.58, 0.89) | 0.70 | ( 0.56, 0.88) | -0.02 | (-0.03,-0.01) | |
| Region | | | | | | | | | | | | | | 0.3001 |
| North America | 434 | 37 | 8.5 | 432 | 17 | 3.9 | 0.0051 | 0.46 | ( 0.26, 0.81) | 0.44 | ( 0.24, 0.79) | -0.05 | (-0.08,-0.01) | |
| Latin America | 931 | 57 | 6.1 | 944 | 45 | 4.8 | 0.2212 | 0.79 | ( 0.54, 1.15) | 0.78 | ( 0.52, 1.17) | -0.01 | (-0.03, 0.01) | |
| Europe | 1334 | 86 | 6.4 | 1361 | 62 | 4.6 | 0.0289 | 0.70 | ( 0.51, 0.97) | 0.69 | ( 0.49, 0.96) | -0.02 | (-0.04, 0.00) | |
| Asia | 405 | 31 | 7.7 | 413 | 33 | 8.0 | 0.8994 | 1.03 | ( 0.64, 1.65) | 1.03 | ( 0.62, 1.73) | 0.00 | (-0.03, 0.04) | |
| Other | 171 | 18 | 10.5 | 180 | 14 | 7.8 | 0.3577 | 0.73 | ( 0.38, 1.42) | 0.71 | ( 0.34, 1.48) | -0.03 | (-0.09, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.0286 |
| Diabetic | 1739 | 125 | 7.2 | 1779 | 112 | 6.3 | 0.2759 | 0.87 | ( 0.68, 1.12) | 0.86 | ( 0.66, 1.12) | -0.01 | (-0.03, 0.01) | |
| Non-Diabetic | 1536 | 104 | 6.8 | 1551 | 59 | 3.8 | 0.0002 | 0.56 | ( 0.41, 0.76) | 0.54 | ( 0.39, 0.75) | -0.03 | (-0.05,-0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3163 |
| <30 | 1975 | 139 | 7.0 | 1930 | 109 | 5.6 | 0.0613 | 0.79 | ( 0.62, 1.01) | 0.78 | ( 0.60, 1.01) | -0.01 | (-0.03, 0.00) | |
| >=30 | 1300 | 90 | 6.9 | 1400 | 62 | 4.4 | 0.0063 | 0.65 | ( 0.47, 0.89) | 0.63 | ( 0.45, 0.88) | -0.02 | (-0.04,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.6142 |
| <130 | 1684 | 111 | 6.6 | 1687 | 78 | 4.6 | 0.0104 | 0.69 | ( 0.52, 0.92) | 0.68 | ( 0.50, 0.91) | -0.02 | (-0.04, 0.00) | |
| >=130 | 1591 | 118 | 7.4 | 1643 | 93 | 5.7 | 0.0464 | 0.77 | ( 0.59, <1.00) | 0.75 | ( 0.57, 1.00) | -0.02 | (-0.03, 0.00) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.4019 |
| <75 | 1653 | 133 | 8.0 | 1612 | 86 | 5.3 | 0.0015 | 0.66 ( 0.51, | 0.85) | 0.63 ( 0.48, | 0.84) | -0.03 (-0.04,-0.01) | |
| 75 to <85 | 1005 | 62 | 6.2 | 1085 | 59 | 5.4 | 0.4850 | 0.88 ( 0.63, | 1.25) | 0.88 ( 0.61, | 1.27) | -0.01 (-0.03, 0.01) | |
| >=85 | 617 | 34 | 5.5 | 633 | 26 | 4.1 | 0.2520 | 0.75 ( 0.45, | 1.23) | 0.74 ( 0.44, | 1.24) | -0.01 (-0.04, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.5832 |
| <30 | 250 | 31 | 12.4 | 263 | 28 | 10.6 | 0.7559 | 0.93 ( 0.58, | 1.49) | 0.92 ( 0.53, | 1.59) | -0.01 (-0.06, 0.05) | |
| 30 to <45 | 898 | 71 | 7.9 | 909 | 50 | 5.5 | 0.0367 | 0.69 ( 0.49, | 0.98) | 0.67 ( 0.46, | 0.98) | -0.02 (-0.05, 0.00) | |
| >=45 | 2126 | 127 | 6.0 | 2158 | 93 | 4.3 | 0.0117 | 0.72 ( 0.55, | 0.93) | 0.70 ( 0.53, | 0.93) | -0.02 (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.2546 |
| Normal (<30) | 1216 | 77 | 6.3 | 1243 | 52 | 4.2 | 0.0158 | 0.66 ( 0.47, | 0.93) | 0.64 ( 0.45, | 0.92) | -0.02 (-0.04, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 107 | 6.9 | 1546 | 74 | 4.8 | 0.0102 | 0.69 ( 0.52, | 0.92) | 0.67 ( 0.49, | 0.91) | -0.02 (-0.04,-0.01) | |
| Macroalbuminuria (>300) | 500 | 44 | 8.8 | 525 | 45 | 8.6 | 0.9459 | 0.99 ( 0.67, | 1.46) | 0.98 ( 0.64, | 1.53) | 0.00 (-0.04, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.6793 |
| Low, moderate or high | 2430 | 145 | 6.0 | 2495 | 108 | 4.3 | 0.0077 | 0.72 ( 0.57, | 0.92) | 0.71 ( 0.55, | 0.91) | -0.02 (-0.03, 0.00) | |
| Very high | 834 | 83 | 10.0 | 820 | 63 | 7.7 | 0.1214 | 0.78 ( 0.57, | 1.07) | 0.76 ( 0.54, | 1.08) | -0.02 (-0.05, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.1691 |
| No | 572 | 48 | 8.4 | 578 | 45 | 7.8 | 0.7181 | 0.93 ( 0.63, | 1.37) | 0.92 ( 0.60, | 1.41) | -0.01 (-0.04, 0.03) | |
| Yes | 2703 | 181 | 6.7 | 2752 | 126 | 4.6 | 0.0006 | 0.68 ( 0.55, | 0.85) | 0.66 ( 0.52, | 0.84) | -0.02 (-0.03,-0.01) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.9051 |
| No | 344 | 29 | 8.4 | 349 | 22 | 6.3 | 0.2997 | 0.75 ( 0.44, | 1.29) | 0.74 ( 0.41, | 1.31) | -0.02 (-0.06, 0.02) | |
| Yes | 2931 | 200 | 6.8 | 2981 | 149 | 5.0 | 0.0024 | 0.73 ( 0.59, | 0.89) | 0.71 ( 0.57, | 0.89) | -0.02 (-0.03,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.2285 |
| No | 275 | 13 | 4.7 | 307 | 16 | 5.2 | 0.7596 | 1.12 ( 0.55, 2.28) | 1.12 ( 0.53, 2.39) | 0.01 (-0.03, 0.04) | |
| Yes | 3000 | 216 | 7.2 | 3023 | 155 | 5.1 | 0.0007 | 0.71 ( 0.58, 0.87) | 0.69 ( 0.56, 0.86) | -0.02 (-0.03,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Iron deficiency anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 53 | 1.6 | 3330 | 32 | 1.0 | 0.0169 | 0.59 | ( 0.38, 0.91) | 0.59 | ( 0.38, 0.91) | -0.01 | (-0.01, 0.00) | |
| Study | | | | | | | | | | | | | | 0.6182 |
| 1245.110 | 2001 | 42 | 2.1 | 2052 | 24 | 1.2 | 0.0194 | 0.56 | ( 0.34, 0.92) | 0.55 | ( 0.33, 0.91) | -0.01 | (-0.02, 0.00) | |
| 1245.121 | 1274 | 11 | 0.9 | 1278 | 8 | 0.6 | 0.4855 | 0.72 | ( 0.29, 1.80) | 0.72 | ( 0.29, 1.80) | 0.00 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.0967 |
| Male | 2023 | 36 | 1.8 | 2068 | 16 | 0.8 | 0.0040 | 0.43 | ( 0.24, 0.78) | 0.43 | ( 0.24, 0.78) | -0.01 | (-0.02, 0.00) | |
| Female | 1252 | 17 | 1.4 | 1262 | 16 | 1.3 | 0.8287 | 0.93 | ( 0.47, 1.83) | 0.93 | ( 0.47, 1.84) | 0.00 | (-0.01, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.7084 |
| <65 | 766 | 7 | 0.9 | 705 | 3 | 0.4 | 0.2466 | 0.46 | ( 0.12, 1.77) | 0.46 | ( 0.12, 1.78) | 0.00 | (-0.01, 0.00) | |
| >=65 | 2509 | 46 | 1.8 | 2625 | 29 | 1.1 | 0.0301 | 0.60 | ( 0.38, 0.96) | 0.60 | ( 0.37, 0.96) | -0.01 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.7185 |
| North America | 434 | 10 | 2.3 | 432 | 5 | 1.2 | 0.2075 | 0.52 | ( 0.19, 1.46) | 0.52 | ( 0.18, 1.47) | -0.01 | (-0.03, 0.01) | |
| Latin America | 931 | 9 | 1.0 | 944 | 4 | 0.4 | 0.1662 | 0.45 | ( 0.14, 1.44) | 0.44 | ( 0.14, 1.45) | -0.01 | (-0.01, 0.00) | |
| Europe | 1334 | 18 | 1.3 | 1361 | 11 | 0.8 | 0.1746 | 0.60 | ( 0.29, 1.26) | 0.60 | ( 0.28, 1.27) | -0.01 | (-0.01, 0.00) | |
| Asia | 405 | 15 | 3.7 | 413 | 9 | 2.2 | 0.1744 | 0.57 | ( 0.25, 1.29) | 0.56 | ( 0.24, 1.30) | -0.02 | (-0.04, 0.01) | |
| Other | 171 | 1 | 0.6 | 180 | 3 | 1.7 | 0.4075 | 2.20 | ( 0.32, 14.94) | 2.22 | ( 0.32, 15.34) | 0.01 | (-0.01, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.1090 |
| Diabetic | 1739 | 34 | 2.0 | 1779 | 15 | 0.8 | 0.0045 | 0.43 | ( 0.23, 0.78) | 0.42 | ( 0.23, 0.78) | -0.01 | (-0.02, 0.00) | |
| Non-Diabetic | 1536 | 19 | 1.2 | 1551 | 17 | 1.1 | 0.7130 | 0.89 | ( 0.46, 1.70) | 0.88 | ( 0.46, 1.71) | 0.00 | (-0.01, 0.01) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.3427 |
| <30 | 1975 | 33 | 1.7 | 1930 | 16 | 0.8 | 0.0161 | 0.49 | ( 0.27, 0.89) | 0.49 | ( 0.27, 0.89) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1300 | 20 | 1.5 | 1400 | 16 | 1.1 | 0.3915 | 0.75 | ( 0.39, 1.45) | 0.75 | ( 0.39, 1.45) | 0.00 | (-0.01, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.1744 |
| <130 | 1684 | 22 | 1.3 | 1687 | 18 | 1.1 | 0.5088 | 0.81 | ( 0.44, 1.51) | 0.81 | ( 0.43, 1.52) | 0.00 | (-0.01, 0.00) | |
| >=130 | 1591 | 31 | 1.9 | 1643 | 14 | 0.9 | 0.0084 | 0.44 | ( 0.24, 0.83) | 0.44 | ( 0.23, 0.82) | -0.01 | (-0.02, 0.00) | |

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Preferred term: Iron deficiency anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | 0.9000 |
| <75 | 1653 | 31 | 1.9 | 1612 | 18 | 1.1 | 0.0687 | 0.59 ( 0.33, 1.05) | 0.58 ( 0.33, 1.05) | -0.01 | (-0.02, 0.00) | |
| 75 to <85 | 1005 | 12 | 1.2 | 1085 | 9 | 0.8 | 0.4090 | 0.70 ( 0.29, 1.65) | 0.69 ( 0.29, 1.66) | 0.00 | (-0.01, 0.01) | |
| >=85 | 617 | 10 | 1.6 | 633 | 5 | 0.8 | 0.1926 | 0.51 ( 0.18, 1.43) | 0.51 ( 0.18, 1.43) | -0.01 | (-0.02, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | 0.5343 |
| <30 | 250 | 9 | 3.6 | 263 | 3 | 1.1 | 0.0934 | 0.37 ( 0.11, 1.24) | 0.36 ( 0.11, 1.25) | -0.02 | (-0.05, 0.00) | |
| 30 to <45 | 898 | 16 | 1.8 | 909 | 8 | 0.9 | 0.0981 | 0.51 ( 0.22, 1.15) | 0.50 ( 0.22, 1.15) | -0.01 | (-0.02, 0.00) | |
| >=45 | 2126 | 28 | 1.3 | 2158 | 21 | 1.0 | 0.2759 | 0.73 ( 0.42, 1.28) | 0.73 ( 0.41, 1.29) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | 0.7151 |
| Normal (<30) | 1216 | 21 | 1.7 | 1243 | 10 | 0.8 | 0.0398 | 0.46 ( 0.22, 0.98) | 0.46 ( 0.22, 0.98) | -0.01 | (-0.02, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 26 | 1.7 | 1546 | 18 | 1.2 | 0.2137 | 0.69 ( 0.38, 1.25) | 0.68 ( 0.37, 1.25) | -0.01 | (-0.01, 0.00) | |
| Macroalbuminuria (>300) | 500 | 6 | 1.2 | 525 | 4 | 0.8 | 0.5002 | 0.66 ( 0.20, 2.21) | 0.66 ( 0.20, 2.22) | 0.00 | (-0.02, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | 0.9196 |
| Low, moderate or high | 2430 | 36 | 1.5 | 2495 | 22 | 0.9 | 0.0476 | 0.59 ( 0.35, >1.00) | 0.59 ( 0.35, 1.00) | -0.01 | (-0.01, 0.00) | |
| Very high | 834 | 17 | 2.0 | 820 | 10 | 1.2 | 0.2099 | 0.62 ( 0.29, 1.32) | 0.61 ( 0.28, 1.33) | -0.01 | (-0.02, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | 0.4094 |
| No | 572 | 8 | 1.4 | 578 | 7 | 1.2 | 0.7852 | 0.87 ( 0.32, 2.39) | 0.87 ( 0.31, 2.41) | 0.00 | (-0.01, 0.01) | |
| Yes | 2703 | 45 | 1.7 | 2752 | 25 | 0.9 | 0.0121 | 0.54 ( 0.33, 0.88) | 0.54 ( 0.33, 0.88) | -0.01 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | 0.8225 |
| No | 344 | 6 | 1.7 | 349 | 3 | 0.9 | 0.3146 | 0.51 ( 0.14, 1.94) | 0.51 ( 0.14, 1.92) | -0.01 | (-0.03, 0.01) | |
| Yes | 2931 | 47 | 1.6 | 2981 | 29 | 1.0 | 0.0289 | 0.60 ( 0.38, 0.95) | 0.60 ( 0.38, 0.95) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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Preferred term: Iron deficiency anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.9175 |
| No | 275 | 5 | 1.8 | 307 | 3 | 1.0 | 0.3859 | 0.55 ( 0.14, 2.15) | 0.55 ( 0.14, 2.15) | -0.01 (-0.03, 0.01) | |
| Yes | 3000 | 48 | 1.6 | 3023 | 29 | 1.0 | 0.0255 | 0.60 ( 0.38, 0.94) | 0.59 ( 0.37, 0.94) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Thrombocytopenia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 38 | 1.2 | 3330 | 28 | 0.8 | 0.1888 | 0.72 ( 0.44, 1.18) | 0.72 ( 0.44, 1.18) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Pruritus

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 59 | 1.8 | 3330 | 68 | 2.0 | 0.4798 | 1.13 ( 0.80, 1.60) | 1.14 ( 0.80, 1.61) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Skin and subcutaneous tissue disorders
Preferred term: Skin ulcer

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 46 | 1.4 | 3330 | 44 | 1.3 | 0.7644 | 0.94 ( 0.62, 1.42) | 0.94 ( 0.62, 1.42) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Insomnia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 74 | 2.3 | 3330 | 80 | 2.4 | 0.7042 | 1.06 ( 0.78, 1.45) | 1.06 ( 0.77, 1.47) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Depression

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 56 | 1.7 | 3330 | 61 | 1.8 | 0.7120 | 1.07 ( 0.75, 1.53) | 1.07 ( 0.74, 1.55) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Psychiatric disorders
Preferred term: Anxiety

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 52 | 1.6 | 3330 | 39 | 1.2 | 0.1424 | 0.74 ( 0.49, 1.11) | 0.73 ( 0.48, 1.11) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Eye disorders
Preferred term: Cataract

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 60 | 1.8 | 3330 | 75 | 2.3 | 0.2370 | 1.22 ( 0.88, | 1.71) | 1.23 ( 0.87, | 1.73) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Hepatobiliary disorders
Preferred term: Cholelithiasis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 45 | 1.4 | 3330 | 29 | 0.9 | 0.0514 | 0.63 ( 0.40, 1.01) | 0.63 ( 0.39, 1.01) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Reproductive system and breast disorders
Preferred term: Benign prostatic hyperplasia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 48 | 1.5 | 3330 | 50 | 1.5 | 0.9128 | 1.02 ( 0.69, | 1.51) | 1.02 ( 0.69, | 1.52) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Endocrine disorders
Preferred term: Hypothyroidism

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 62 | 1.9 | 3330 | 44 | 1.3 | 0.0647 | 0.70 ( 0.48, 1.02) | 0.69 ( 0.47, 1.02) | -0.01 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 1 Proportion of patients with any adverse event occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Ear and labyrinth disorders
Preferred term: Vertigo

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 46 | 1.4 | 3330 | 44 | 1.3 | 0.7580 | 0.94 ( 0.62, 1.41) | 0.94 ( 0.62, 1.42) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 891 | 27.2 | 3330 | 720 | 21.6 | <0.0001 | 0.80 | ( 0.73, | 0.87) | 0.74 | ( 0.66, 0.83) | -0.06 | (-0.08,-0.03) | |
| Study | | | | | | | | | | | | | | | 0.8039 |
| 1245.110 | 2001 | 516 | 25.8 | 2052 | 417 | 20.3 | <0.0001 | 0.79 | ( 0.70, | 0.88) | 0.73 | ( 0.63, 0.85) | -0.05 | (-0.08,-0.03) | |
| 1245.121 | 1274 | 375 | 29.4 | 1278 | 303 | 23.7 | 0.0011 | 0.81 | ( 0.71, | 0.92) | 0.75 | ( 0.62, 0.89) | -0.06 | (-0.09,-0.02) | |
| Sex | | | | | | | | | | | | | | | 0.6958 |
| Male | 2023 | 571 | 28.2 | 2068 | 458 | 22.1 | <0.0001 | 0.78 | ( 0.71, | 0.87) | 0.72 | ( 0.63, 0.83) | -0.06 | (-0.09,-0.03) | |
| Female | 1252 | 320 | 25.6 | 1262 | 262 | 20.8 | 0.0046 | 0.81 | ( 0.70, | 0.94) | 0.76 | ( 0.63, 0.92) | -0.05 | (-0.08,-0.01) | |
| Age [years] | | | | | | | | | | | | | | | 0.1963 |
| <65 | 766 | 209 | 27.3 | 705 | 169 | 24.0 | 0.1550 | 0.88 | ( 0.74, | 1.05) | 0.84 | ( 0.67, 1.07) | -0.03 | (-0.08, 0.01) | |
| >=65 | 2509 | 682 | 27.2 | 2625 | 551 | 21.0 | <0.0001 | 0.77 | ( 0.70, | 0.85) | 0.71 | ( 0.63, 0.81) | -0.06 | (-0.09,-0.04) | |
| Region | | | | | | | | | | | | | | | 0.5969 |
| North America | 434 | 86 | 19.8 | 432 | 76 | 17.6 | 0.4019 | 0.89 | ( 0.67, | 1.17) | 0.86 | ( 0.61, 1.22) | -0.02 | (-0.07, 0.03) | |
| Latin America | 931 | 263 | 28.2 | 944 | 220 | 23.3 | 0.0136 | 0.82 | ( 0.71, | 0.96) | 0.77 | ( 0.63, 0.95) | -0.05 | (-0.09,-0.01) | |
| Europe | 1334 | 380 | 28.5 | 1361 | 302 | 22.2 | 0.0002 | 0.78 | ( 0.68, | 0.89) | 0.72 | ( 0.60, 0.85) | -0.06 | (-0.10,-0.03) | |
| Asia | 405 | 122 | 30.1 | 413 | 84 | 20.3 | 0.0016 | 0.68 | ( 0.54, | 0.87) | 0.60 | ( 0.43, 0.82) | -0.10 | (-0.15,-0.04) | |
| Other | 171 | 40 | 23.4 | 180 | 38 | 21.1 | 0.5610 | 0.89 | ( 0.60, | 1.31) | 0.86 | ( 0.52, 1.43) | -0.03 | (-0.11, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | 0.8018 |
| Diabetic | 1739 | 496 | 28.5 | 1779 | 407 | 22.9 | 0.0001 | 0.80 | ( 0.72, | 0.90) | 0.74 | ( 0.64, 0.87) | -0.06 | (-0.09,-0.03) | |
| Non-Diabetic | 1536 | 395 | 25.7 | 1551 | 313 | 20.2 | 0.0003 | 0.79 | ( 0.69, | 0.89) | 0.73 | ( 0.62, 0.86) | -0.06 | (-0.08,-0.03) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | 0.2980 |
| <30 | 1975 | 547 | 27.7 | 1930 | 408 | 21.1 | <0.0001 | 0.76 | ( 0.68, | 0.86) | 0.70 | ( 0.61, 0.81) | -0.07 | (-0.09,-0.04) | |
| >=30 | 1300 | 344 | 26.5 | 1400 | 312 | 22.3 | 0.0096 | 0.84 | ( 0.73, | 0.96) | 0.79 | ( 0.66, 0.94) | -0.04 | (-0.08,-0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | 0.9341 |
| <130 | 1684 | 492 | 29.2 | 1687 | 393 | 23.3 | 0.0001 | 0.80 | ( 0.71, | 0.90) | 0.74 | ( 0.63, 0.86) | -0.06 | (-0.09,-0.03) | |
| >=130 | 1591 | 399 | 25.1 | 1643 | 327 | 19.9 | 0.0004 | 0.79 | ( 0.70, | 0.90) | 0.74 | ( 0.63, 0.88) | -0.05 | (-0.08,-0.02) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.0739 |
| <75 | 1653 | 456 | 27.6 | 1612 | 389 | 24.1 | 0.0258 | 0.88 | ( 0.78, 0.98) | 0.84 | ( 0.71, 0.98) | -0.03 | (-0.06, 0.00) | |
| 75 to <85 | 1005 | 271 | 27.0 | 1085 | 210 | 19.4 | <0.0001 | 0.72 | ( 0.61, 0.84) | 0.65 | ( 0.53, 0.80) | -0.08 | (-0.11,-0.04) | |
| >=85 | 617 | 164 | 26.6 | 633 | 121 | 19.1 | 0.0016 | 0.72 | ( 0.58, 0.88) | 0.65 | ( 0.50, 0.85) | -0.07 | (-0.12,-0.03) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1411 |
| <30 | 250 | 84 | 33.6 | 263 | 85 | 32.3 | 0.6759 | 0.95 | ( 0.74, 1.21) | 0.92 | ( 0.64, 1.34) | -0.02 | (-0.10, 0.06) | |
| 30 to <45 | 898 | 254 | 28.3 | 909 | 218 | 24.0 | 0.0379 | 0.85 | ( 0.73, 0.99) | 0.80 | ( 0.65, 0.99) | -0.04 | (-0.08, 0.00) | |
| >=45 | 2126 | 553 | 26.0 | 2158 | 417 | 19.3 | <0.0001 | 0.74 | ( 0.67, 0.83) | 0.68 | ( 0.59, 0.79) | -0.07 | (-0.09,-0.04) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.6732 |
| Normal (<30) | 1216 | 289 | 23.8 | 1243 | 225 | 18.1 | 0.0006 | 0.76 | ( 0.65, 0.89) | 0.71 | ( 0.58, 0.86) | -0.06 | (-0.09,-0.02) | |
| Microalbuminuria (30 to <=300) | 1548 | 431 | 27.8 | 1546 | 357 | 23.1 | 0.0026 | 0.83 | ( 0.74, 0.94) | 0.78 | ( 0.66, 0.92) | -0.05 | (-0.08,-0.02) | |
| Macroalbuminuria (>300) | 500 | 167 | 33.4 | 525 | 138 | 26.3 | 0.0115 | 0.78 | ( 0.65, 0.95) | 0.71 | ( 0.54, 0.93) | -0.07 | (-0.13,-0.02) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.1764 |
| Low, moderate or high | 2430 | 615 | 25.3 | 2495 | 486 | 19.5 | <0.0001 | 0.77 | ( 0.69, 0.86) | 0.72 | ( 0.63, 0.82) | -0.06 | (-0.08,-0.03) | |
| Very high | 834 | 272 | 32.6 | 820 | 234 | 28.5 | 0.0663 | 0.87 | ( 0.75, 1.01) | 0.82 | ( 0.67, 1.01) | -0.04 | (-0.09, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.0247 |
| No | 572 | 155 | 27.1 | 578 | 152 | 26.3 | 0.7590 | 0.97 | ( 0.80, 1.18) | 0.96 | ( 0.74, 1.25) | -0.01 | (-0.06, 0.04) | |
| Yes | 2703 | 736 | 27.2 | 2752 | 568 | 20.6 | <0.0001 | 0.76 | ( 0.69, 0.84) | 0.70 | ( 0.61, 0.79) | -0.07 | (-0.09,-0.04) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.1480 |
| No | 344 | 89 | 25.9 | 349 | 86 | 24.6 | 0.7033 | 0.95 | ( 0.74, 1.23) | 0.94 | ( 0.66, 1.32) | -0.01 | (-0.08, 0.05) | |
| Yes | 2931 | 802 | 27.4 | 2981 | 634 | 21.3 | <0.0001 | 0.78 | ( 0.71, 0.85) | 0.72 | ( 0.64, 0.81) | -0.06 | (-0.08,-0.04) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | | 0.2198 |
| No | 275 | 49 | 17.8 | 307 | 34 | 11.1 | 0.0210 | 0.62 | ( 0.42, | 0.94) | 0.58 | ( 0.36, 0.93) | -0.07 | (-0.12,-0.01) | |
| Yes | 3000 | 842 | 28.1 | 3023 | 686 | 22.7 | <0.0001 | 0.81 | ( 0.74, | 0.88) | 0.75 | ( 0.67, 0.85) | -0.05 | (-0.08,-0.03) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 118 | 3.6 | 3330 | 82 | 2.5 | 0.0068 | 0.68 | ( 0.52, | 0.90) | 0.67 | ( 0.51, | 0.90) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | | | 0.3202 |
| 1245.110 | 2001 | 72 | 3.6 | 2052 | 56 | 2.7 | 0.1137 | 0.76 | ( 0.54, | 1.07) | 0.75 | ( 0.53, | 1.07) | -0.01 | (-0.02, 0.00) | |
| 1245.121 | 1274 | 46 | 3.6 | 1278 | 26 | 2.0 | 0.0162 | 0.56 | ( 0.35, | 0.91) | 0.55 | ( 0.34, | 0.90) | -0.02 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.4711 |
| Male | 2023 | 76 | 3.8 | 2068 | 49 | 2.4 | 0.0099 | 0.63 | ( 0.44, | 0.90) | 0.62 | ( 0.43, | 0.89) | -0.01 | (-0.02, 0.00) | |
| Female | 1252 | 42 | 3.4 | 1262 | 33 | 2.6 | 0.2716 | 0.78 | ( 0.50, | 1.22) | 0.77 | ( 0.49, | 1.23) | -0.01 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | | | | 0.9452 |
| <65 | 766 | 25 | 3.3 | 705 | 16 | 2.3 | 0.2474 | 0.70 | ( 0.37, | 1.29) | 0.69 | ( 0.36, | 1.30) | -0.01 | (-0.03, 0.01) | |
| >=65 | 2509 | 93 | 3.7 | 2625 | 66 | 2.5 | 0.0138 | 0.68 | ( 0.50, | 0.93) | 0.67 | ( 0.49, | 0.92) | -0.01 | (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | | | | 0.0959 |
| North America | 434 | 80 | 18.4 | 432 | 63 | 14.6 | 0.1257 | 0.79 | ( 0.58, | 1.07) | 0.75 | ( 0.53, | 1.08) | -0.04 | (-0.09, 0.01) | |
| Latin America | 931 | 16 | 1.7 | 944 | 5 | 0.5 | 0.0138 | 0.31 | ( 0.11, | 0.83) | 0.30 | ( 0.11, | 0.83) | -0.01 | (-0.02, 0.00) | |
| Europe | 1334 | 8 | 0.6 | 1361 | 10 | 0.7 | 0.6516 | 1.24 | ( 0.49, | 3.12) | 1.24 | ( 0.49, | 3.15) | 0.00 | ( 0.00, 0.01) | |
| Asia | 405 | 6 | 1.5 | 413 | 4 | 1.0 | 0.5279 | 0.68 | ( 0.20, | 2.29) | 0.68 | ( 0.20, | 2.28) | -0.01 | (-0.02, 0.01) | |
| Other | 171 | 8 | 4.7 | 180 | 0 | 0 | 0.0077 | 0.11 | ( 0.01, | 0.81) | 0.10 | ( 0.01, | 0.80) | -0.05 | (-0.08,-0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | | 0.8198 |
| Diabetic | 1739 | 72 | 4.1 | 1779 | 49 | 2.8 | 0.0239 | 0.66 | ( 0.47, | 0.95) | 0.66 | ( 0.45, | 0.95) | -0.01 | (-0.03, 0.00) | |
| Non-Diabetic | 1536 | 46 | 3.0 | 1551 | 33 | 2.1 | 0.1266 | 0.71 | ( 0.46, | 1.10) | 0.70 | ( 0.45, | 1.11) | -0.01 | (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.7102 |
| <30 | 1975 | 62 | 3.1 | 1930 | 39 | 2.0 | 0.0271 | 0.64 | ( 0.43, | 0.95) | 0.63 | ( 0.42, | 0.95) | -0.01 | (-0.02, 0.00) | |
| >=30 | 1300 | 56 | 4.3 | 1400 | 43 | 3.1 | 0.0880 | 0.71 | ( 0.48, | 1.05) | 0.70 | ( 0.47, | 1.06) | -0.01 | (-0.03, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.4916 |
| <130 | 1684 | 67 | 4.0 | 1687 | 50 | 3.0 | 0.1066 | 0.74 | ( 0.52, | 1.07) | 0.74 | ( 0.51, | 1.07) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1591 | 51 | 3.2 | 1643 | 32 | 1.9 | 0.0247 | 0.61 | ( 0.39, | 0.94) | 0.60 | ( 0.38, | 0.94) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.1751 |
| <75 | 1653 | 59 | 3.6 | 1612 | 49 | 3.0 | 0.3882 | 0.85 | ( 0.58, 1.23) | 0.84 | ( 0.57, 1.24) | -0.01 | (-0.02, 0.01) | |
| 75 to <85 | 1005 | 31 | 3.1 | 1085 | 21 | 1.9 | 0.0925 | 0.63 | ( 0.36, 1.09) | 0.62 | ( 0.35, 1.09) | -0.01 | (-0.02, 0.00) | |
| >=85 | 617 | 28 | 4.5 | 633 | 12 | 1.9 | 0.0079 | 0.42 | ( 0.21, 0.81) | 0.41 | ( 0.20, 0.81) | -0.03 | (-0.05,-0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.6039 |
| <30 | 250 | 17 | 6.8 | 263 | 13 | 4.9 | 0.5165 | 0.80 | ( 0.40, 1.58) | 0.78 | ( 0.37, 1.65) | -0.01 | (-0.05, 0.03) | |
| 30 to <45 | 898 | 30 | 3.3 | 909 | 25 | 2.8 | 0.4637 | 0.82 | ( 0.49, 1.39) | 0.82 | ( 0.48, 1.40) | -0.01 | (-0.02, 0.01) | |
| >=45 | 2126 | 71 | 3.3 | 2158 | 44 | 2.0 | 0.0087 | 0.61 | ( 0.42, 0.89) | 0.60 | ( 0.41, 0.88) | -0.01 | (-0.02, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3024 |
| Normal (<30) | 1216 | 30 | 2.5 | 1243 | 21 | 1.7 | 0.1738 | 0.68 | ( 0.39, 1.19) | 0.68 | ( 0.39, 1.19) | -0.01 | (-0.02, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 60 | 3.9 | 1546 | 48 | 3.1 | 0.2455 | 0.80 | ( 0.55, 1.17) | 0.80 | ( 0.54, 1.17) | -0.01 | (-0.02, 0.01) | |
| Macroalbuminuria (>300) | 500 | 28 | 5.6 | 525 | 13 | 2.5 | 0.0114 | 0.44 | ( 0.23, 0.85) | 0.43 | ( 0.22, 0.84) | -0.03 | (-0.06,-0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.2443 |
| Low, moderate or high | 2430 | 77 | 3.2 | 2495 | 48 | 1.9 | 0.0057 | 0.61 | ( 0.43, 0.87) | 0.60 | ( 0.42, 0.86) | -0.01 | (-0.02, 0.00) | |
| Very high | 834 | 41 | 4.9 | 820 | 34 | 4.1 | 0.4797 | 0.85 | ( 0.55, 1.33) | 0.85 | ( 0.53, 1.35) | -0.01 | (-0.03, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.3483 |
| No | 572 | 32 | 5.6 | 578 | 27 | 4.7 | 0.4836 | 0.84 | ( 0.51, 1.38) | 0.83 | ( 0.49, 1.40) | -0.01 | (-0.03, 0.02) | |
| Yes | 2703 | 86 | 3.2 | 2752 | 55 | 2.0 | 0.0059 | 0.63 | ( 0.45, 0.88) | 0.62 | ( 0.44, 0.87) | -0.01 | (-0.02, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.9039 |
| No | 344 | 15 | 4.4 | 349 | 11 | 3.2 | 0.3748 | 0.71 | ( 0.33, 1.52) | 0.70 | ( 0.32, 1.54) | -0.01 | (-0.04, 0.02) | |
| Yes | 2931 | 103 | 3.5 | 2981 | 71 | 2.4 | 0.0097 | 0.68 | ( 0.50, 0.91) | 0.67 | ( 0.49, 0.91) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.7201 |
| No | 275 | 5 | 1.8 | 307 | 3 | 1.0 | 0.3777 | 0.53 | ( 0.13, 2.21) | 0.53 | ( 0.12, 2.23) | -0.01 | (-0.03, 0.01) | |
| Yes | 3000 | 113 | 3.8 | 3023 | 79 | 2.6 | 0.0106 | 0.69 | ( 0.52, 0.92) | 0.68 | ( 0.51, 0.92) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Atrial fibrillation

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 97 | 3.0 | 3330 | 92 | 2.8 | 0.6176 | 0.93 | ( 0.70, 1.23) | 0.93 | ( 0.70, 1.24) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 63 | 1.9 | 3330 | 65 | 2.0 | 0.9479 | 1.01 | ( 0.72, 1.43) | 1.01 | ( 0.71, 1.44) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Ventricular tachycardia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 61 | 1.9 | 3330 | 61 | 1.8 | 0.9546 | 0.99 | ( 0.70, 1.41) | 0.99 | ( 0.69, 1.42) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

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System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 59 | 1.8 | 3330 | 39 | 1.2 | 0.0350 | 0.65 | ( 0.44, | 0.97) | 0.65 | ( 0.43, | 0.97) | -0.01 | (-0.01, 0.00) | |
| Study | | | | | | | | | | | | | | | | 0.5533 |
| 1245.110 | 2001 | 32 | 1.6 | 2052 | 19 | 0.9 | 0.0546 | 0.58 | ( 0.33, | 1.02) | 0.58 | ( 0.32, | 1.02) | -0.01 | (-0.01, 0.00) | |
| 1245.121 | 1274 | 27 | 2.1 | 1278 | 20 | 1.6 | 0.2978 | 0.74 | ( 0.42, | 1.31) | 0.73 | ( 0.41, | 1.32) | -0.01 | (-0.02, 0.00) | |
| Sex | | | | | | | | | | | | | | | | 0.4716 |
| Male | 2023 | 38 | 1.9 | 2068 | 28 | 1.4 | 0.1840 | 0.72 | ( 0.44, | 1.17) | 0.72 | ( 0.44, | 1.17) | -0.01 | (-0.01, 0.00) | |
| Female | 1252 | 21 | 1.7 | 1262 | 11 | 0.9 | 0.0745 | 0.52 | ( 0.25, | 1.08) | 0.52 | ( 0.25, | 1.08) | -0.01 | (-0.02, 0.00) | |
| Age [years] | | | | | | | | | | | | | | | | 0.3305 |
| <65 | 766 | 16 | 2.1 | 705 | 13 | 1.8 | 0.7550 | 0.89 | ( 0.43, | 1.84) | 0.89 | ( 0.42, | 1.86) | 0.00 | (-0.02, 0.01) | |
| >=65 | 2509 | 43 | 1.7 | 2625 | 26 | 1.0 | 0.0244 | 0.58 | ( 0.36, | 0.94) | 0.57 | ( 0.35, | 0.94) | -0.01 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | | | 0.5098 |
| North America | 434 | 32 | 7.4 | 432 | 27 | 6.3 | 0.5143 | 0.85 | ( 0.52, | 1.39) | 0.84 | ( 0.49, | 1.42) | -0.01 | (-0.04, 0.02) | |
| Latin America | 931 | 4 | 0.4 | 944 | 2 | 0.2 | 0.4327 | 0.54 | ( 0.11, | 2.56) | 0.54 | ( 0.11, | 2.56) | 0.00 | (-0.01, 0.00) | |
| Europe | 1334 | 16 | 1.2 | 1361 | 5 | 0.4 | 0.0149 | 0.31 | ( 0.11, | 0.84) | 0.31 | ( 0.11, | 0.84) | -0.01 | (-0.01, 0.00) | |
| Asia | 405 | 7 | 1.7 | 413 | 5 | 1.2 | 0.5267 | 0.70 | ( 0.23, | 2.15) | 0.69 | ( 0.22, | 2.18) | -0.01 | (-0.02, 0.01) | |
| Other | 171 | 0 | 0 | 180 | 0 | 0 | 0.9906 | 0.98 | ( 0.06, | 15.54) | 0.98 | ( 0.06, | 15.88) | 0.00 | (-0.02, 0.02) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | | | 0.2161 |
| Diabetic | 1739 | 40 | 2.3 | 1779 | 31 | 1.7 | 0.2430 | 0.76 | ( 0.48, | 1.21) | 0.75 | ( 0.47, | 1.21) | -0.01 | (-0.01, 0.00) | |
| Non-Diabetic | 1536 | 19 | 1.2 | 1551 | 8 | 0.5 | 0.0319 | 0.42 | ( 0.18, | 0.95) | 0.42 | ( 0.18, | 0.95) | -0.01 | (-0.01, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | | | 0.4474 |
| <30 | 1975 | 32 | 1.6 | 1930 | 17 | 0.9 | 0.0409 | 0.55 | ( 0.31, | 0.98) | 0.55 | ( 0.30, | 0.98) | -0.01 | (-0.01, 0.00) | |
| >=30 | 1300 | 27 | 2.1 | 1400 | 22 | 1.6 | 0.3125 | 0.75 | ( 0.43, | 1.31) | 0.75 | ( 0.42, | 1.32) | -0.01 | (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | | | 0.9138 |
| <130 | 1684 | 33 | 2.0 | 1687 | 21 | 1.2 | 0.1040 | 0.64 | ( 0.37, | 1.10) | 0.64 | ( 0.37, | 1.10) | -0.01 | (-0.02, 0.00) | |
| >=130 | 1591 | 26 | 1.6 | 1643 | 18 | 1.1 | 0.1850 | 0.67 | ( 0.37, | 1.22) | 0.67 | ( 0.36, | 1.22) | -0.01 | (-0.01, 0.00) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
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System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.2142 |
| <75 | 1653 | 39 | 2.4 | 1612 | 22 | 1.4 | 0.0372 | 0.58 | ( 0.35, | 0.97) | 0.57 | ( 0.34, | 0.97) | -0.01 | (-0.02, 0.00) | |
| 75 to <85 | 1005 | 10 | 1.0 | 1085 | 13 | 1.2 | 0.6623 | 1.20 | ( 0.53, | 2.73) | 1.20 | ( 0.52, | 2.76) | 0.00 | (-0.01, 0.01) | |
| >=85 | 617 | 10 | 1.6 | 633 | 4 | 0.6 | 0.0959 | 0.39 | ( 0.12, | 1.23) | 0.38 | ( 0.12, | 1.23) | -0.01 | (-0.02, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.5235 |
| <30 | 250 | 12 | 4.8 | 263 | 5 | 1.9 | 0.0588 | 0.37 | ( 0.13, | 1.09) | 0.36 | ( 0.12, | 1.06) | -0.03 | (-0.06, 0.00) | |
| 30 to <45 | 898 | 14 | 1.6 | 909 | 11 | 1.2 | 0.5288 | 0.78 | ( 0.35, | 1.70) | 0.77 | ( 0.35, | 1.72) | 0.00 | (-0.01, 0.01) | |
| >=45 | 2126 | 33 | 1.6 | 2158 | 23 | 1.1 | 0.1690 | 0.69 | ( 0.41, | 1.17) | 0.69 | ( 0.40, | 1.18) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.9526 |
| Normal (<30) | 1216 | 11 | 0.9 | 1243 | 8 | 0.6 | 0.4669 | 0.72 | ( 0.29, | 1.77) | 0.71 | ( 0.29, | 1.78) | 0.00 | (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 32 | 2.1 | 1546 | 21 | 1.4 | 0.1312 | 0.66 | ( 0.38, | 1.14) | 0.65 | ( 0.38, | 1.14) | -0.01 | (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 500 | 16 | 3.2 | 525 | 10 | 1.9 | 0.1856 | 0.59 | ( 0.27, | 1.30) | 0.59 | ( 0.26, | 1.30) | -0.01 | (-0.03, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.5207 |
| Low, moderate or high | 2430 | 32 | 1.3 | 2495 | 24 | 1.0 | 0.2522 | 0.74 | ( 0.43, | 1.25) | 0.73 | ( 0.43, | 1.25) | 0.00 | (-0.01, 0.00) | |
| Very high | 834 | 27 | 3.2 | 820 | 15 | 1.8 | 0.0682 | 0.56 | ( 0.30, | 1.05) | 0.56 | ( 0.29, | 1.05) | -0.01 | (-0.03, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | | | 0.5353 |
| No | 572 | 12 | 2.1 | 578 | 10 | 1.7 | 0.6432 | 0.82 | ( 0.36, | 1.89) | 0.82 | ( 0.35, | 1.91) | 0.00 | (-0.02, 0.01) | |
| Yes | 2703 | 47 | 1.7 | 2752 | 29 | 1.1 | 0.0322 | 0.61 | ( 0.38, | 0.96) | 0.60 | ( 0.38, | 0.96) | -0.01 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.3148 |
| No | 344 | 7 | 2.0 | 349 | 2 | 0.6 | 0.1063 | 0.33 | ( 0.08, | 1.36) | 0.32 | ( 0.08, | 1.36) | -0.01 | (-0.03, 0.00) | |
| Yes | 2931 | 52 | 1.8 | 2981 | 37 | 1.2 | 0.0961 | 0.70 | ( 0.46, | 1.07) | 0.70 | ( 0.46, | 1.07) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.6325 |
| No | 275 | 4 | 1.5 | 307 | 2 | 0.7 | 0.3264 | 0.44 | ( 0.08, 2.39) | 0.43 | ( 0.08, 2.40) | -0.01 | (-0.02, 0.01) | |
| Yes | 3000 | 55 | 1.8 | 3023 | 37 | 1.2 | 0.0550 | 0.67 | ( 0.44, 1.01) | 0.66 | ( 0.44, 1.01) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure chronic

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 51 | 1.6 | 3330 | 50 | 1.5 | 0.8579 | 0.97 | ( 0.66, 1.42) | 0.96 | ( 0.65, 1.43) | 0.00 | (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 31 | 0.9 | 3330 | 47 | 1.4 | 0.0817 | 1.49 | ( 0.95, 2.34) | 1.50 | ( 0.95, 2.36) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Angina unstable

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 23 | 0.7 | 3330 | 34 | 1.0 | 0.1632 | 1.45 | ( 0.86, 2.46) | 1.46 | ( 0.86, 2.48) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 173 | 5.3 | 3330 | 166 | 5.0 | 0.5762 | 0.94 | ( 0.77, 1.16) | 0.94 | ( 0.75, 1.17) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Urinary tract infection

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 43 | 1.3 | 3330 | 52 | 1.6 | 0.4017 | 1.19 | ( 0.79, 1.77) | 1.19 | ( 0.79, 1.79) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: COVID-19

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 49 | 1.5 | 3330 | 46 | 1.4 | 0.6686 | 0.92 | ( 0.62, 1.37) | 0.92 | ( 0.61, 1.37) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Sepsis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 35 | 1.1 | 3330 | 42 | 1.3 | 0.4735 | 1.18 | ( 0.75, 1.84) | 1.18 | ( 0.75, 1.85) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 171 | 5.2 | 3330 | 129 | 3.9 | 0.0082 | 0.74 | ( 0.59, 0.93) | 0.73 | ( 0.58, 0.92) | -0.01 | (-0.02, 0.00) | |
| Study | | | | | | | | | | | | | | 0.8684 |
| 1245.110 | 2001 | 117 | 5.8 | 2052 | 90 | 4.4 | 0.0347 | 0.75 | ( 0.57, 0.98) | 0.74 | ( 0.56, 0.98) | -0.01 | (-0.03, 0.00) | |
| 1245.121 | 1274 | 54 | 4.2 | 1278 | 39 | 3.1 | 0.1097 | 0.72 | ( 0.48, 1.08) | 0.71 | ( 0.47, 1.08) | -0.01 | (-0.03, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.4217 |
| Male | 2023 | 108 | 5.3 | 2068 | 76 | 3.7 | 0.0101 | 0.69 | ( 0.52, 0.92) | 0.68 | ( 0.50, 0.91) | -0.02 | (-0.03, 0.00) | |
| Female | 1252 | 63 | 5.0 | 1262 | 53 | 4.2 | 0.3052 | 0.83 | ( 0.58, 1.19) | 0.82 | ( 0.57, 1.20) | -0.01 | (-0.02, 0.01) | |
| Age [years] | | | | | | | | | | | | | | 0.3768 |
| <65 | 766 | 31 | 4.0 | 705 | 26 | 3.7 | 0.7167 | 0.91 | ( 0.55, 1.52) | 0.91 | ( 0.53, 1.54) | 0.00 | (-0.02, 0.02) | |
| >=65 | 2509 | 140 | 5.6 | 2625 | 103 | 3.9 | 0.0053 | 0.70 | ( 0.55, 0.90) | 0.69 | ( 0.53, 0.90) | -0.02 | (-0.03, 0.00) | |
| Region | | | | | | | | | | | | | | 0.5886 |
| North America | 434 | 62 | 14.3 | 432 | 55 | 12.7 | 0.5000 | 0.89 | ( 0.64, 1.25) | 0.87 | ( 0.59, 1.29) | -0.02 | (-0.06, 0.03) | |
| Latin America | 931 | 40 | 4.3 | 944 | 30 | 3.2 | 0.2094 | 0.74 | ( 0.47, 1.18) | 0.74 | ( 0.45, 1.19) | -0.01 | (-0.03, 0.01) | |
| Europe | 1334 | 48 | 3.6 | 1361 | 29 | 2.1 | 0.0226 | 0.59 | ( 0.38, 0.93) | 0.58 | ( 0.37, 0.93) | -0.01 | (-0.03, 0.00) | |
| Asia | 405 | 10 | 2.5 | 413 | 5 | 1.2 | 0.1577 | 0.47 | ( 0.16, 1.37) | 0.47 | ( 0.16, 1.38) | -0.01 | (-0.03, 0.01) | |
| Other | 171 | 11 | 6.4 | 180 | 10 | 5.6 | 0.6768 | 0.84 | ( 0.38, 1.89) | 0.83 | ( 0.35, 1.98) | -0.01 | (-0.06, 0.04) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.9233 |
| Diabetic | 1739 | 105 | 6.0 | 1779 | 79 | 4.4 | 0.0314 | 0.73 | ( 0.55, 0.97) | 0.72 | ( 0.53, 0.97) | -0.02 | (-0.03, 0.00) | |
| Non-Diabetic | 1536 | 66 | 4.3 | 1551 | 50 | 3.2 | 0.1166 | 0.75 | ( 0.52, 1.08) | 0.74 | ( 0.51, 1.08) | -0.01 | (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.2162 |
| <30 | 1975 | 90 | 4.6 | 1930 | 56 | 2.9 | 0.0058 | 0.63 | ( 0.46, 0.88) | 0.62 | ( 0.44, 0.87) | -0.02 | (-0.03, 0.00) | |
| >=30 | 1300 | 81 | 6.2 | 1400 | 73 | 5.2 | 0.2683 | 0.84 | ( 0.62, 1.14) | 0.83 | ( 0.60, 1.15) | -0.01 | (-0.03, 0.01) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7319 |
| <130 | 1684 | 97 | 5.8 | 1687 | 75 | 4.4 | 0.0763 | 0.77 | ( 0.57, 1.03) | 0.76 | ( 0.55, 1.03) | -0.01 | (-0.03, 0.00) | |
| >=130 | 1591 | 74 | 4.7 | 1643 | 54 | 3.3 | 0.0488 | 0.71 | ( 0.50, >1.00) | 0.70 | ( 0.49, 1.00) | -0.01 | (-0.03, 0.00) | |

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System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.4141 |
| <75 | 1653 | 105 | 6.4 | 1612 | 83 | 5.1 | 0.1313 | 0.81 | ( 0.61, 1.07) | 0.80 | ( 0.59, 1.07) | -0.01 | (-0.03, 0.00) | |
| 75 to <85 | 1005 | 42 | 4.2 | 1085 | 34 | 3.1 | 0.2055 | 0.75 | ( 0.48, 1.17) | 0.74 | ( 0.47, 1.18) | -0.01 | (-0.03, 0.01) | |
| >=85 | 617 | 24 | 3.9 | 633 | 12 | 1.9 | 0.0361 | 0.49 | ( 0.25, 0.97) | 0.48 | ( 0.24, 0.97) | -0.02 | (-0.04, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.0774 |
| <30 | 250 | 22 | 8.8 | 263 | 29 | 11.0 | 0.3281 | 1.31 | ( 0.76, 2.24) | 1.34 | ( 0.74, 2.43) | 0.03 | (-0.03, 0.08) | |
| 30 to <45 | 898 | 62 | 6.9 | 909 | 42 | 4.6 | 0.0357 | 0.67 | ( 0.46, 0.98) | 0.65 | ( 0.43, 0.97) | -0.02 | (-0.04, 0.00) | |
| >=45 | 2126 | 87 | 4.1 | 2158 | 58 | 2.7 | 0.0103 | 0.65 | ( 0.47, 0.91) | 0.64 | ( 0.46, 0.90) | -0.01 | (-0.03, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.3386 |
| Normal (<30) | 1216 | 53 | 4.4 | 1243 | 45 | 3.6 | 0.3478 | 0.83 | ( 0.56, 1.23) | 0.82 | ( 0.55, 1.24) | -0.01 | (-0.02, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 88 | 5.7 | 1546 | 56 | 3.6 | 0.0058 | 0.63 | ( 0.46, 0.88) | 0.62 | ( 0.44, 0.87) | -0.02 | (-0.04,-0.01) | |
| Macroalbuminuria (>300) | 500 | 28 | 5.6 | 525 | 28 | 5.3 | 0.8682 | 0.96 | ( 0.57, 1.60) | 0.96 | ( 0.56, 1.64) | 0.00 | (-0.03, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.3616 |
| Low, moderate or high | 2430 | 102 | 4.2 | 2495 | 73 | 2.9 | 0.0149 | 0.69 | ( 0.52, 0.93) | 0.69 | ( 0.50, 0.93) | -0.01 | (-0.02, 0.00) | |
| Very high | 834 | 67 | 8.0 | 820 | 56 | 6.8 | 0.3744 | 0.86 | ( 0.61, 1.21) | 0.85 | ( 0.58, 1.22) | -0.01 | (-0.04, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.5868 |
| No | 572 | 32 | 5.6 | 578 | 27 | 4.7 | 0.4905 | 0.84 | ( 0.51, 1.38) | 0.83 | ( 0.49, 1.41) | -0.01 | (-0.03, 0.02) | |
| Yes | 2703 | 139 | 5.1 | 2752 | 102 | 3.7 | 0.0094 | 0.72 | ( 0.56, 0.92) | 0.71 | ( 0.55, 0.92) | -0.01 | (-0.03, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4340 |
| No | 344 | 25 | 7.3 | 349 | 15 | 4.3 | 0.0880 | 0.59 | ( 0.32, 1.09) | 0.57 | ( 0.29, 1.10) | -0.03 | (-0.07, 0.00) | |
| Yes | 2931 | 146 | 5.0 | 2981 | 114 | 3.8 | 0.0279 | 0.77 | ( 0.60, 0.97) | 0.76 | ( 0.59, 0.97) | -0.01 | (-0.02, 0.00) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
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Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.2146 |
| No | 275 | 13 | 4.7 | 307 | 6 | 2.0 | 0.0613 | 0.41 | ( 0.16, 1.08) | 0.40 | ( 0.15, 1.07) | -0.03 | (-0.06, 0.00) | |
| Yes | 3000 | 158 | 5.3 | 3023 | 123 | 4.1 | 0.0263 | 0.77 | ( 0.61, 0.97) | 0.76 | ( 0.60, 0.97) | -0.01 | (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal impairment

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 69 | 2.1 | 3330 | 71 | 2.1 | 0.9485 | 1.01 | ( 0.73, 1.40) | 1.01 | ( 0.72, 1.41) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 42 | 1.3 | 3330 | 16 | 0.5 | 0.0005 | 0.37 | ( 0.21, 0.67) | 0.37 | ( 0.21, 0.66) | -0.01 | (-0.01, 0.00) | |
| Study | | | | | | | | | | | | | | 0.6660 |
| 1245.110 | 2001 | 26 | 1.3 | 2052 | 9 | 0.4 | 0.0031 | 0.34 | ( 0.16, 0.72) | 0.33 | ( 0.16, 0.72) | -0.01 | (-0.01, 0.00) | |
| 1245.121 | 1274 | 16 | 1.3 | 1278 | 7 | 0.5 | 0.0584 | 0.44 | ( 0.18, 1.06) | 0.43 | ( 0.18, 1.06) | -0.01 | (-0.01, 0.00) | |
| Sex | | | | | | | | | | | | | | 0.6265 |
| Male | 2023 | 28 | 1.4 | 2068 | 12 | 0.6 | 0.0090 | 0.42 | ( 0.21, 0.82) | 0.42 | ( 0.21, 0.82) | -0.01 | (-0.01, 0.00) | |
| Female | 1252 | 14 | 1.1 | 1262 | 4 | 0.3 | 0.0205 | 0.31 | ( 0.11, 0.88) | 0.30 | ( 0.11, 0.88) | -0.01 | (-0.01, 0.00) | |
| Age [years] | | | | | | | | | | | | | | 0.5527 |
| <65 | 766 | 12 | 1.6 | 705 | 3 | 0.4 | 0.0285 | 0.27 | ( 0.08, 0.95) | 0.27 | ( 0.07, 0.95) | -0.01 | (-0.02, 0.00) | |
| >=65 | 2509 | 30 | 1.2 | 2625 | 13 | 0.5 | 0.0059 | 0.41 | ( 0.22, 0.79) | 0.41 | ( 0.21, 0.79) | -0.01 | (-0.01, 0.00) | |
| Region | | | | | | | | | | | | | | 0.4975 |
| North America | 434 | 6 | 1.4 | 432 | 2 | 0.5 | 0.1817 | 0.39 | ( 0.09, 1.65) | 0.38 | ( 0.09, 1.65) | -0.01 | (-0.02, 0.00) | |
| Latin America | 931 | 17 | 1.8 | 944 | 3 | 0.3 | 0.0015 | 0.17 | ( 0.05, 0.59) | 0.17 | ( 0.05, 0.59) | -0.02 | (-0.02,-0.01) | |
| Europe | 1334 | 15 | 1.1 | 1361 | 9 | 0.7 | 0.2043 | 0.59 | ( 0.26, 1.34) | 0.59 | ( 0.26, 1.35) | 0.00 | (-0.01, 0.00) | |
| Asia | 405 | 1 | 0.2 | 413 | 1 | 0.2 | 0.9928 | 0.99 | ( 0.14, 7.22) | 0.99 | ( 0.14, 7.17) | 0.00 | (-0.01, 0.01) | |
| Other | 171 | 3 | 1.8 | 180 | 1 | 0.6 | 0.3495 | 0.41 | ( 0.06, 2.78) | 0.41 | ( 0.06, 2.81) | -0.01 | (-0.04, 0.01) | |
| Baseline Diabetes Status | | | | | | | | | | | | | | 0.6890 |
| Diabetic | 1739 | 21 | 1.2 | 1779 | 9 | 0.5 | 0.0235 | 0.42 | ( 0.19, 0.91) | 0.42 | ( 0.19, 0.91) | -0.01 | (-0.01, 0.00) | |
| Non-Diabetic | 1536 | 21 | 1.4 | 1551 | 7 | 0.5 | 0.0073 | 0.33 | ( 0.14, 0.77) | 0.33 | ( 0.14, 0.77) | -0.01 | (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | | 0.8027 |
| <30 | 1975 | 21 | 1.1 | 1930 | 7 | 0.4 | 0.0094 | 0.34 | ( 0.15, 0.80) | 0.34 | ( 0.14, 0.80) | -0.01 | (-0.01, 0.00) | |
| >=30 | 1300 | 21 | 1.6 | 1400 | 9 | 0.6 | 0.0153 | 0.39 | ( 0.18, 0.86) | 0.39 | ( 0.18, 0.86) | -0.01 | (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | | 0.7127 |
| <130 | 1684 | 21 | 1.2 | 1687 | 7 | 0.4 | 0.0080 | 0.33 | ( 0.14, 0.78) | 0.33 | ( 0.14, 0.78) | -0.01 | (-0.01, 0.00) | |
| >=130 | 1591 | 21 | 1.3 | 1643 | 9 | 0.5 | 0.0223 | 0.42 | ( 0.19, 0.90) | 0.41 | ( 0.19, 0.90) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | | Odds ratio | (95% CI) | | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | | | 0.4287 |
| <75 | 1653 | 24 | 1.5 | 1612 | 8 | 0.5 | 0.0059 | 0.34 | ( 0.16, | 0.76) | 0.34 | ( 0.15, | 0.76) | -0.01 | (-0.02, 0.00) | |
| 75 to <85 | 1005 | 13 | 1.3 | 1085 | 4 | 0.4 | 0.0189 | 0.28 | ( 0.09, | 0.87) | 0.28 | ( 0.09, | 0.87) | -0.01 | (-0.02, 0.00) | |
| >=85 | 617 | 5 | 0.8 | 633 | 4 | 0.6 | 0.7258 | 0.80 | ( 0.23, | 2.77) | 0.80 | ( 0.23, | 2.79) | 0.00 | (-0.01, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | | | 0.7170 |
| <30 | 250 | 15 | 6.0 | 263 | 5 | 1.9 | 0.0146 | 0.31 | ( 0.11, | 0.84) | 0.29 | ( 0.10, | 0.82) | -0.04 | (-0.08,-0.01) | |
| 30 to <45 | 898 | 14 | 1.6 | 909 | 7 | 0.8 | 0.1187 | 0.49 | ( 0.20, | 1.22) | 0.49 | ( 0.20, | 1.22) | -0.01 | (-0.02, 0.00) | |
| >=45 | 2126 | 13 | 0.6 | 2158 | 4 | 0.2 | 0.0258 | 0.30 | ( 0.10, | 0.92) | 0.30 | ( 0.10, | 0.92) | 0.00 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | | | 0.7138 |
| Normal (<30) | 1216 | 12 | 1.0 | 1243 | 6 | 0.5 | 0.1442 | 0.49 | ( 0.18, | 1.30) | 0.49 | ( 0.18, | 1.30) | -0.01 | (-0.01, 0.00) | |
| Microalbuminuria (30 to <=300) | 1548 | 21 | 1.4 | 1546 | 6 | 0.4 | 0.0039 | 0.29 | ( 0.12, | 0.71) | 0.28 | ( 0.11, | 0.71) | -0.01 | (-0.02, 0.00) | |
| Macroalbuminuria (>300) | 500 | 9 | 1.8 | 525 | 4 | 0.8 | 0.1453 | 0.43 | ( 0.13, | 1.39) | 0.42 | ( 0.13, | 1.39) | -0.01 | (-0.02, 0.00) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | | | 0.8654 |
| Low, moderate or high | 2430 | 19 | 0.8 | 2495 | 7 | 0.3 | 0.0150 | 0.36 | ( 0.15, | 0.85) | 0.36 | ( 0.15, | 0.85) | -0.01 | (-0.01, 0.00) | |
| Very high | 834 | 23 | 2.8 | 820 | 9 | 1.1 | 0.0138 | 0.40 | ( 0.18, | 0.85) | 0.39 | ( 0.18, | 0.85) | -0.02 | (-0.03, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | | | 0.9305 |
| No | 572 | 10 | 1.7 | 578 | 4 | 0.7 | 0.0970 | 0.39 | ( 0.12, | 1.24) | 0.38 | ( 0.12, | 1.24) | -0.01 | (-0.02, 0.00) | |
| Yes | 2703 | 32 | 1.2 | 2752 | 12 | 0.4 | 0.0020 | 0.37 | ( 0.19, | 0.71) | 0.36 | ( 0.19, | 0.71) | -0.01 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | | | 0.4425 |
| No | 344 | 5 | 1.5 | 349 | 3 | 0.9 | 0.4847 | 0.62 | ( 0.16, | 2.40) | 0.62 | ( 0.16, | 2.40) | -0.01 | (-0.02, 0.01) | |
| Yes | 2931 | 37 | 1.3 | 2981 | 13 | 0.4 | 0.0005 | 0.35 | ( 0.18, | 0.65) | 0.34 | ( 0.18, | 0.65) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | | | | 0.7407 |
| No | 275 | 2 | 0.7 | 307 | 1 | 0.3 | 0.5350 | 0.53 | ( 0.07, 4.03) | 0.53 | ( 0.07, 4.05) | 0.00 | (-0.02, 0.01) | |
| Yes | 3000 | 40 | 1.3 | 3023 | 15 | 0.5 | 0.0006 | 0.37 | ( 0.21, 0.67) | 0.37 | ( 0.20, 0.67) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Chronic kidney disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Overall | 3275 | 36 | 1.1 | 3330 | 24 | 0.7 | 0.1011 | 0.65 | ( 0.39, 1.09) | 0.65 | ( 0.39, 1.09) | 0.00 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Ischaemic stroke

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 47 | 1.4 | 3330 | 49 | 1.5 | 0.9126 | 1.02 | ( 0.69, 1.52) | 1.02 | ( 0.68, 1.53) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Nervous system disorders
Preferred term: Syncope

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 23 | 0.7 | 3330 | 34 | 1.0 | 0.1620 | 1.45 | ( 0.86, 2.46) | 1.46 | ( 0.86, 2.48) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Vascular disorders
Preferred term: Hypotension

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 32 | 1.0 | 3330 | 40 | 1.2 | 0.3804 | 1.23 | ( 0.77, 1.95) | 1.23 | ( 0.77, 1.97) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Chronic obstructive pulmonary disease

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 41 | 1.3 | 3330 | 37 | 1.1 | 0.5866 | 0.88 ( 0.57, 1.38) | 0.88 ( 0.56, 1.38) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 85 | 2.6 | 3330 | 94 | 2.8 | 0.5773 | 1.09 | ( 0.81, 1.45) | 1.09 | ( 0.81, 1.47) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 36 | 1.1 | 3330 | 45 | 1.4 | 0.3566 | 1.23 ( 0.79, 1.90) | 1.23 ( 0.79, 1.91) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 2 Proportion of patients with serious adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Blood and lymphatic system disorders
Preferred term: Anaemia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 38 | 1.2 | 3330 | 29 | 0.9 | 0.2345 | 0.75 | ( 0.46, 1.21) | 0.75 | ( 0.46, 1.21) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 374 | 11.4 | 3330 | 288 | 8.6 | 0.0002 | 0.76 ( 0.66, 0.88) | | 0.74 ( 0.63, 0.86) | | -0.03 (-0.04,-0.01) | |
| Study | | | | | | | | | | | | | 0.0758 |
| 1245.110 | 2001 | 216 | 10.8 | 2052 | 149 | 7.3 | <0.0001 | 0.67 ( 0.55, 0.82) | | 0.65 ( 0.52, 0.81) | | -0.04 (-0.05,-0.02) | |
| 1245.121 | 1274 | 158 | 12.4 | 1278 | 139 | 10.9 | 0.2296 | 0.88 ( 0.71, 1.09) | | 0.86 ( 0.68, 1.10) | | -0.02 (-0.04, 0.01) | |
| Sex | | | | | | | | | | | | | 0.2117 |
| Male | 2023 | 234 | 11.6 | 2068 | 194 | 9.4 | 0.0226 | 0.81 ( 0.68, 0.97) | | 0.79 ( 0.65, 0.97) | | -0.02 (-0.04, 0.00) | |
| Female | 1252 | 140 | 11.2 | 1262 | 94 | 7.4 | 0.0013 | 0.67 ( 0.52, 0.86) | | 0.64 ( 0.49, 0.84) | | -0.04 (-0.06,-0.01) | |
| Age [years] | | | | | | | | | | | | | 0.5080 |
| <65 | 766 | 99 | 12.9 | 705 | 75 | 10.6 | 0.1839 | 0.83 ( 0.62, 1.10) | | 0.81 ( 0.59, 1.11) | | -0.02 (-0.06, 0.01) | |
| >=65 | 2509 | 275 | 11.0 | 2625 | 213 | 8.1 | 0.0005 | 0.74 ( 0.62, 0.88) | | 0.72 ( 0.59, 0.87) | | -0.03 (-0.04,-0.01) | |
| Region | | | | | | | | | | | | | 0.4836 |
| North America | 434 | 33 | 7.6 | 432 | 30 | 6.9 | 0.7122 | 0.91 ( 0.57, 1.47) | | 0.91 ( 0.54, 1.52) | | -0.01 (-0.04, 0.03) | |
| Latin America | 931 | 122 | 13.1 | 944 | 103 | 10.9 | 0.1401 | 0.83 ( 0.65, 1.06) | | 0.81 ( 0.61, 1.07) | | -0.02 (-0.05, 0.01) | |
| Europe | 1334 | 152 | 11.4 | 1361 | 106 | 7.8 | 0.0016 | 0.69 ( 0.54, 0.87) | | 0.66 ( 0.51, 0.85) | | -0.04 (-0.06,-0.01) | |
| Asia | 405 | 50 | 12.3 | 413 | 31 | 7.5 | 0.0246 | 0.62 ( 0.40, 0.94) | | 0.58 ( 0.36, 0.94) | | -0.05 (-0.09,-0.01) | |
| Other | 171 | 17 | 9.9 | 180 | 18 | 10.0 | 0.9960 | 1.00 ( 0.53, 1.87) | | 1.00 ( 0.50, 2.01) | | 0.00 (-0.06, 0.06) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.6496 |
| Diabetic | 1739 | 222 | 12.8 | 1779 | 167 | 9.4 | 0.0015 | 0.74 ( 0.61, 0.89) | | 0.71 ( 0.57, 0.88) | | -0.03 (-0.05,-0.01) | |
| Non-Diabetic | 1536 | 152 | 9.9 | 1551 | 121 | 7.8 | 0.0412 | 0.79 ( 0.63, 0.99) | | 0.77 ( 0.60, 0.99) | | -0.02 (-0.04, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.9319 |
| <30 | 1975 | 233 | 11.8 | 1930 | 171 | 8.9 | 0.0028 | 0.75 ( 0.62, 0.91) | | 0.73 ( 0.59, 0.90) | | -0.03 (-0.05,-0.01) | |
| >=30 | 1300 | 141 | 10.8 | 1400 | 117 | 8.4 | 0.0225 | 0.76 ( 0.60, 0.96) | | 0.74 ( 0.57, 0.96) | | -0.03 (-0.05, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.8881 |
| <130 | 1684 | 222 | 13.2 | 1687 | 170 | 10.1 | 0.0056 | 0.77 ( 0.64, 0.93) | | 0.74 ( 0.60, 0.92) | | -0.03 (-0.05,-0.01) | |
| >=130 | 1591 | 152 | 9.6 | 1643 | 118 | 7.2 | 0.0149 | 0.75 ( 0.60, 0.95) | | 0.73 ( 0.57, 0.94) | | -0.02 (-0.04, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | 0.7275 |
| <75 | 1653 | 205 | 12.4 | 1612 | 155 | 9.6 | 0.0122 | 0.78 ( 0.64, | 0.95) | 0.75 ( 0.61, | 0.94) | -0.03 (-0.05,-0.01) | |
| 75 to <85 | 1005 | 110 | 10.9 | 1085 | 83 | 7.6 | 0.0090 | 0.70 ( 0.53, | 0.92) | 0.67 ( 0.50, | 0.91) | -0.03 (-0.06,-0.01) | |
| >=85 | 617 | 59 | 9.6 | 633 | 50 | 7.9 | 0.2947 | 0.83 ( 0.58, | 1.18) | 0.81 ( 0.55, | 1.20) | -0.02 (-0.05, 0.01) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | 0.3889 |
| <30 | 250 | 40 | 16.0 | 263 | 40 | 15.2 | 0.8339 | 0.96 ( 0.64, | 1.44) | 0.95 ( 0.59, | 1.53) | -0.01 (-0.07, 0.06) | |
| 30 to <45 | 898 | 108 | 12.0 | 909 | 87 | 9.6 | 0.0935 | 0.80 ( 0.61, | 1.04) | 0.77 ( 0.57, | 1.04) | -0.02 (-0.05, 0.00) | |
| >=45 | 2126 | 226 | 10.6 | 2158 | 161 | 7.5 | 0.0004 | 0.71 ( 0.58, | 0.86) | 0.68 ( 0.55, | 0.84) | -0.03 (-0.05,-0.01) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | 0.6299 |
| Normal (<30) | 1216 | 120 | 9.9 | 1243 | 84 | 6.8 | 0.0052 | 0.69 ( 0.52, | 0.90) | 0.66 ( 0.50, | 0.89) | -0.03 (-0.05,-0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 177 | 11.4 | 1546 | 142 | 9.2 | 0.0433 | 0.81 ( 0.65, | 0.99) | 0.79 ( 0.62, | 0.99) | -0.02 (-0.04, 0.00) | |
| Macroalbuminuria (>300) | 500 | 75 | 15.0 | 525 | 62 | 11.8 | 0.1269 | 0.78 ( 0.57, | 1.07) | 0.75 ( 0.53, | 1.08) | -0.03 (-0.07, 0.01) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | 0.6099 |
| Low, moderate or high | 2430 | 249 | 10.2 | 2495 | 190 | 7.6 | 0.0014 | 0.75 ( 0.62, | 0.89) | 0.72 ( 0.59, | 0.88) | -0.03 (-0.04,-0.01) | |
| Very high | 834 | 123 | 14.7 | 820 | 98 | 12.0 | 0.0911 | 0.81 ( 0.63, | 1.04) | 0.78 ( 0.59, | 1.04) | -0.03 (-0.06, 0.00) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | 0.2143 |
| No | 572 | 61 | 10.7 | 578 | 57 | 9.9 | 0.6505 | 0.92 ( 0.66, | 1.30) | 0.92 ( 0.63, | 1.34) | -0.01 (-0.04, 0.03) | |
| Yes | 2703 | 313 | 11.6 | 2752 | 231 | 8.4 | <0.0001 | 0.73 ( 0.62, | 0.85) | 0.70 ( 0.59, | 0.84) | -0.03 (-0.05,-0.02) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | 0.2600 |
| No | 344 | 33 | 9.6 | 349 | 33 | 9.5 | 0.9057 | 0.97 ( 0.62, | 1.54) | 0.97 ( 0.58, | 1.61) | 0.00 (-0.05, 0.04) | |
| Yes | 2931 | 341 | 11.6 | 2981 | 255 | 8.6 | <0.0001 | 0.74 ( 0.63, | 0.86) | 0.71 ( 0.60, | 0.84) | -0.03 (-0.05,-0.02) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.4118 |
| No | 275 | 10 | 3.6 | 307 | 12 | 3.9 | 0.8755 | 1.07 ( 0.47, 2.42) | 1.07 ( 0.46, 2.51) | 0.00 (-0.03, 0.03) | |
| Yes | 3000 | 364 | 12.1 | 3023 | 276 | 9.1 | 0.0002 | 0.75 ( 0.65, 0.87) | 0.73 ( 0.62, 0.86) | -0.03 (-0.05,-0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure congestive

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 45 | 1.4 | 3330 | 32 | 1.0 | 0.1200 | 0.70 ( 0.45, 1.10) | 0.70 ( 0.44, 1.10) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Acute myocardial infarction

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 43 | 1.3 | 3330 | 39 | 1.2 | 0.5936 | 0.89 ( 0.58, 1.37) | 0.89 ( 0.57, 1.37) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Cardiac disorders
Preferred term: Cardiac failure acute

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 36 | 1.1 | 3330 | 27 | 0.8 | 0.2320 | 0.74 ( 0.45, 1.22) | 0.74 ( 0.45, 1.22) | 0.00 (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Pneumonia

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 94 | 2.9 | 3330 | 89 | 2.7 | 0.6209 | 0.93 ( 0.70, 1.24) | 0.93 ( 0.69, 1.25) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Infections and infestations
Preferred term: Sepsis

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 27 | 0.8 | 3330 | 38 | 1.1 | 0.1956 | 1.38 ( 0.85, 2.26) | 1.39 ( 0.84, 2.28) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | | Odds ratio (95% CI) | | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 79 | 2.4 | 3330 | 55 | 1.7 | 0.0280 | 0.68 ( 0.49, 0.96) | | 0.68 ( 0.48, 0.96) | | -0.01 (-0.01, 0.00) | |
| Study | | | | | | | | | | | | | 0.6325 |
| 1245.110 | 2001 | 53 | 2.6 | 2052 | 35 | 1.7 | 0.0395 | 0.64 ( 0.42, 0.98) | | 0.64 ( 0.41, 0.98) | | -0.01 (-0.02, 0.00) | |
| 1245.121 | 1274 | 26 | 2.0 | 1278 | 20 | 1.6 | 0.3664 | 0.77 ( 0.43, 1.37) | | 0.76 ( 0.42, 1.37) | | 0.00 (-0.02, 0.01) | |
| Sex | | | | | | | | | | | | | 0.9794 |
| Male | 2023 | 50 | 2.5 | 2068 | 35 | 1.7 | 0.0807 | 0.68 ( 0.45, 1.05) | | 0.68 ( 0.44, 1.05) | | -0.01 (-0.02, 0.00) | |
| Female | 1252 | 29 | 2.3 | 1262 | 20 | 1.6 | 0.1750 | 0.68 ( 0.39, 1.19) | | 0.67 ( 0.38, 1.20) | | -0.01 (-0.02, 0.00) | |
| Age [years] | | | | | | | | | | | | | 0.1260 |
| <65 | 766 | 12 | 1.6 | 705 | 13 | 1.8 | 0.6777 | 1.18 ( 0.54, 2.57) | | 1.18 ( 0.54, 2.61) | | 0.00 (-0.01, 0.02) | |
| >=65 | 2509 | 67 | 2.7 | 2625 | 42 | 1.6 | 0.0079 | 0.60 ( 0.41, 0.88) | | 0.59 ( 0.40, 0.88) | | -0.01 (-0.02, 0.00) | |
| Region | | | | | | | | | | | | | 0.2443 |
| North America | 434 | 23 | 5.3 | 432 | 22 | 5.1 | 0.8928 | 0.96 ( 0.54, 1.70) | | 0.96 ( 0.53, 1.75) | | 0.00 (-0.03, 0.03) | |
| Latin America | 931 | 19 | 2.0 | 944 | 16 | 1.7 | 0.5978 | 0.84 ( 0.43, 1.62) | | 0.83 ( 0.43, 1.63) | | 0.00 (-0.02, 0.01) | |
| Europe | 1334 | 27 | 2.0 | 1361 | 9 | 0.7 | 0.0021 | 0.33 ( 0.15, 0.69) | | 0.32 ( 0.15, 0.69) | | -0.01 (-0.02, 0.00) | |
| Asia | 405 | 5 | 1.2 | 413 | 4 | 1.0 | 0.6951 | 0.78 ( 0.23, 2.67) | | 0.78 ( 0.22, 2.72) | | 0.00 (-0.02, 0.01) | |
| Other | 171 | 5 | 2.9 | 180 | 4 | 2.2 | 0.6542 | 0.76 ( 0.22, 2.57) | | 0.75 ( 0.21, 2.66) | | -0.01 (-0.04, 0.03) | |
| Baseline Diabetes Status | | | | | | | | | | | | | 0.6510 |
| Diabetic | 1739 | 47 | 2.7 | 1779 | 35 | 2.0 | 0.1470 | 0.73 ( 0.47, 1.12) | | 0.72 ( 0.46, 1.12) | | -0.01 (-0.02, 0.00) | |
| Non-Diabetic | 1536 | 32 | 2.1 | 1551 | 20 | 1.3 | 0.0862 | 0.62 ( 0.36, 1.08) | | 0.61 ( 0.35, 1.08) | | -0.01 (-0.02, 0.00) | |
| Baseline BMI [kg/m²] | | | | | | | | | | | | | 0.9648 |
| <30 | 1975 | 36 | 1.8 | 1930 | 24 | 1.2 | 0.1418 | 0.68 ( 0.41, 1.14) | | 0.68 ( 0.40, 1.14) | | -0.01 (-0.01, 0.00) | |
| >=30 | 1300 | 43 | 3.3 | 1400 | 31 | 2.2 | 0.0857 | 0.67 ( 0.43, 1.06) | | 0.67 ( 0.42, 1.06) | | -0.01 (-0.02, 0.00) | |
| Baseline SBP [mmHg] | | | | | | | | | | | | | 0.5136 |
| <130 | 1684 | 48 | 2.9 | 1687 | 30 | 1.8 | 0.0378 | 0.62 ( 0.40, 0.98) | | 0.62 ( 0.39, 0.98) | | -0.01 (-0.02, 0.00) | |
| >=130 | 1591 | 31 | 1.9 | 1643 | 25 | 1.5 | 0.3607 | 0.78 ( 0.46, 1.32) | | 0.78 ( 0.46, 1.33) | | 0.00 (-0.01, 0.00) | |

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A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

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System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio | (95% CI) | Odds ratio | (95% CI) | Risk diff. | (95% CI) | p-value ** |
| Baseline DBP [mmHg] | | | | | | | | | | | | | | 0.3317 |
| <75 | 1653 | 49 | 3.0 | 1612 | 31 | 1.9 | 0.0531 | 0.65 | ( 0.41, 1.01) | 0.64 | ( 0.41, 1.01) | -0.01 | (-0.02, 0.00) | |
| 75 to <85 | 1005 | 18 | 1.8 | 1085 | 19 | 1.8 | 0.9465 | 0.98 | ( 0.52, 1.86) | 0.98 | ( 0.51, 1.87) | 0.00 | (-0.01, 0.01) | |
| >=85 | 617 | 12 | 1.9 | 633 | 5 | 0.8 | 0.0798 | 0.41 | ( 0.14, 1.15) | 0.40 | ( 0.14, 1.15) | -0.01 | (-0.02, 0.00) | |
| Baseline eGFR (CKD-EPI) [mL/min/1.73m²] | | | | | | | | | | | | | | 0.1317 |
| <30 | 250 | 11 | 4.4 | 263 | 15 | 5.7 | 0.4718 | 1.33 | ( 0.61, 2.93) | 1.35 | ( 0.60, 3.04) | 0.01 | (-0.02, 0.05) | |
| 30 to <45 | 898 | 29 | 3.2 | 909 | 14 | 1.5 | 0.0181 | 0.48 | ( 0.25, 0.89) | 0.47 | ( 0.24, 0.89) | -0.02 | (-0.03, 0.00) | |
| >=45 | 2126 | 39 | 1.8 | 2158 | 26 | 1.2 | 0.0911 | 0.66 | ( 0.40, 1.07) | 0.65 | ( 0.40, 1.07) | -0.01 | (-0.01, 0.00) | |
| Baseline UACR [mg/g] | | | | | | | | | | | | | | 0.0750 |
| Normal (<30) | 1216 | 24 | 2.0 | 1243 | 19 | 1.5 | 0.3983 | 0.77 | ( 0.43, 1.41) | 0.77 | ( 0.42, 1.41) | 0.00 | (-0.01, 0.01) | |
| Microalbuminuria (30 to <=300) | 1548 | 42 | 2.7 | 1546 | 19 | 1.2 | 0.0029 | 0.45 | ( 0.26, 0.77) | 0.45 | ( 0.26, 0.77) | -0.01 | (-0.02,-0.01) | |
| Macroalbuminuria (>300) | 500 | 13 | 2.6 | 525 | 17 | 3.2 | 0.5425 | 1.25 | ( 0.61, 2.55) | 1.26 | ( 0.60, 2.61) | 0.01 | (-0.01, 0.03) | |
| Baseline KDIGO risk category | | | | | | | | | | | | | | 0.4744 |
| Low, moderate or high | 2430 | 47 | 1.9 | 2495 | 30 | 1.2 | 0.0377 | 0.62 | ( 0.39, 0.98) | 0.62 | ( 0.39, 0.98) | -0.01 | (-0.01, 0.00) | |
| Very high | 834 | 32 | 3.8 | 820 | 25 | 3.0 | 0.3886 | 0.80 | ( 0.48, 1.34) | 0.79 | ( 0.46, 1.35) | -0.01 | (-0.03, 0.01) | |
| Baseline use of ACE-inhibitor, ARB or ARNi | | | | | | | | | | | | | | 0.4690 |
| No | 572 | 17 | 3.0 | 578 | 9 | 1.6 | 0.1082 | 0.52 | ( 0.24, 1.17) | 0.52 | ( 0.23, 1.17) | -0.01 | (-0.03, 0.00) | |
| Yes | 2703 | 62 | 2.3 | 2752 | 46 | 1.7 | 0.0977 | 0.73 | ( 0.50, 1.06) | 0.72 | ( 0.49, 1.06) | -0.01 | (-0.01, 0.00) | |
| Baseline use of beta-blockers | | | | | | | | | | | | | | 0.4626 |
| No | 344 | 14 | 4.1 | 349 | 7 | 2.0 | 0.1183 | 0.51 | ( 0.22, 1.21) | 0.50 | ( 0.21, 1.22) | -0.02 | (-0.05, 0.01) | |
| Yes | 2931 | 65 | 2.2 | 2981 | 48 | 1.6 | 0.0867 | 0.73 | ( 0.50, 1.05) | 0.72 | ( 0.49, 1.05) | -0.01 | (-0.01, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Acute kidney injury

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Baseline use of diuretics | | | | | | | | | | | 0.9780 |
| No | 275 | 4 | 1.5 | 307 | 3 | 1.0 | 0.6152 | 0.70 ( 0.18, 2.81) | 0.70 ( 0.17, 2.85) | 0.00 (-0.02, 0.01) | |
| Yes | 3000 | 75 | 2.5 | 3023 | 52 | 1.7 | 0.0347 | 0.69 ( 0.48, 0.98) | 0.68 ( 0.48, 0.97) | -0.01 (-0.02, 0.00) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Renal and urinary disorders
Preferred term: Renal impairment

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 45 | 1.4 | 3330 | 45 | 1.4 | 0.9284 | 0.98 ( 0.65, 1.48) | 0.98 ( 0.65, 1.49) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: General disorders and administration site conditions
Preferred term: Death

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 84 | 2.6 | 3330 | 93 | 2.8 | 0.5739 | 1.09 ( 0.81, 1.45) | 1.09 ( 0.81, 1.47) | 0.00 (-0.01, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

Table R.5.2.5: 3 Proportion of patients with severe adverse events occurring in at least 1% of the patients in either treatment arm in the overall population on PT level by SOC and PT occurring up to the end of the study, overall and by subgroup - TS
System organ class: Injury, poisoning and procedural complications
Preferred term: Fall

| Subgroup | Placebo | | | Empa 10mg | | | Empa 10mg vs Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category | N | n | % | N | n | % | p-value * | Risk ratio (95% CI) | Odds ratio (95% CI) | Risk diff. (95% CI) | p-value ** |
| Overall | 3275 | 24 | 0.7 | 3330 | 34 | 1.0 | 0.2132 | 1.39 ( 0.83, 2.34) | 1.39 ( 0.82, 2.36) | 0.00 ( 0.00, 0.01) | |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
A ratio less than one or risk difference less than zero indicates less risk for Empa 10mg.
A continuity correction by 0.5 is applied in case of any zero cells in contingency table.
MedDRA version: 25.0. * CMH Test for general association for treatment effect. ** Cochran´s-Q test for homogeneity of risk ratios (treatment by subgroup interaction). Risk ratios, odds ratios, risk differences and p-values are adjusted for study.

**R.5.2.6**

R.5.2.6 Medical concepts for adverse events of special interest and other specific AEs

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Broad BIcMQ 'Urinary tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)' | Urinary tract malignancy events (BIcMQ) | 40000010 | | 10004986 | Bladder adenocarcinoma recurrent |
| | | | | 10004987 | Bladder adenocarcinoma stage 0 |
| | | | | 10004988 | Bladder adenocarcinoma stage I |
| | | | | 10004989 | Bladder adenocarcinoma stage II |
| | | | | 10004990 | Bladder adenocarcinoma stage III |
| | | | | 10004991 | Bladder adenocarcinoma stage IV |
| | | | | 10004992 | Bladder adenocarcinoma stage unspecified |
| | | | | 10005003 | Bladder cancer |
| | | | | 10005005 | Bladder cancer recurrent |
| | | | | 10005006 | Bladder cancer stage 0, with cancer in situ |
| | | | | 10005007 | Bladder cancer stage 0, without cancer in situ |
| | | | | 10005008 | Bladder cancer stage I, with cancer in situ |
| | | | | 10005009 | Bladder cancer stage I, without cancer in situ |
| | | | | 10005010 | Bladder cancer stage II |
| | | | | 10005011 | Bladder cancer stage III |
| | | | | 10005012 | Bladder cancer stage IV |
| | | | | 10005056 | Bladder neoplasm |
| | | | | 10005075 | Bladder squamous cell carcinoma recurrent |
| | | | | 10005076 | Bladder squamous cell carcinoma stage 0 |
| | | | | 10005077 | Bladder squamous cell carcinoma stage I |
| | | | | 10005078 | Bladder squamous cell carcinoma stage II |
| | | | | 10005079 | Bladder squamous cell carcinoma stage III |
| | | | | 10005080 | Bladder squamous cell carcinoma stage IV |
| | | | | 10005081 | Bladder squamous cell carcinoma stage unspecified |
| | | | | 10005084 | Bladder transitional cell carcinoma |
| | | | | 10009253 | Clear cell sarcoma of the kidney |
| | | | | 10026426 | Malignant neoplasm of renal pelvis |
| | | | | 10027455 | Metastases to kidney |
| | | | | 10029145 | Nephroblastoma |
| | | | | 10033702 | Papillary tumour of renal pelvis |
| | | | | 10038389 | Renal cancer |
| | | | | 10038390 | Renal cancer recurrent |
| | | | | 10038391 | Renal cancer stage I |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Broad BIcMQ 'Urinary tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)' | Urinary tract malignancy events (BIcMQ) | 40000010 | | 10038392 | Renal cancer stage II |
| | | | | 10038393 | Renal cancer stage III |
| | | | | 10038394 | Renal cancer stage IV |
| | | | | 10038410 | Renal cell carcinoma recurrent |
| | | | | 10038411 | Renal cell carcinoma stage I |
| | | | | 10038412 | Renal cell carcinoma stage II |
| | | | | 10038413 | Renal cell carcinoma stage III |
| | | | | 10038414 | Renal cell carcinoma stage IV |
| | | | | 10039019 | Rhabdoid tumour of the kidney |
| | | | | 10044406 | Transitional cell cancer of renal pelvis and ureter metastatic |
| | | | | 10044407 | Transitional cell cancer of the renal pelvis and ureter |
| | | | | 10044408 | Transitional cell cancer of the renal pelvis and ureter localised |
| | | | | 10044410 | Transitional cell cancer of the renal pelvis and ureter recurrent |
| | | | | 10044411 | Transitional cell cancer of the renal pelvis and ureter regional |
| | | | | 10044412 | Transitional cell carcinoma |
| | | | | 10044426 | Transitional cell carcinoma urethra |
| | | | | 10046392 | Ureteric cancer |
| | | | | 10046393 | Ureteric cancer local |
| | | | | 10046394 | Ureteric cancer metastatic |
| | | | | 10046396 | Ureteric cancer recurrent |
| | | | | 10046397 | Ureteric cancer regional |
| | | | | 10046431 | Urethral cancer |
| | | | | 10046433 | Urethral cancer metastatic |
| | | | | 10046435 | Urethral cancer recurrent |
| | | | | 10049722 | Metastases to bladder |
| | | | | 10050018 | Renal cancer metastatic |
| | | | | 10050513 | Metastatic renal cell carcinoma |
| | | | | 10051690 | Urinary bladder sarcoma |
| | | | | 10051948 | Renal adenoma |
| | | | | 10056251 | Metastases to urinary tract |
| | | | | 10057352 | Metastatic carcinoma of the bladder |
| | | | | 10061183 | Genitourinary tract neoplasm |
| | | | | 10061272 | Malignant urinary tract neoplasm |
| | | | | 10061396 | Urinary tract carcinoma in situ |
| | | | | 10061398 | Urinary tract neoplasm |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Broad BIcMQ 'Urinary tract malignancies (BIcMQ)', Broad BIcMQ 'Renal malignancies (BIcMQ)' | Urinary tract malignancy events (BIcMQ) | 40000010 | | 10061482 | Renal neoplasm |
| | | | | 10061872 | Non-renal cell carcinoma of kidney |
| | | | | 10062221 | Ureteral neoplasm |
| | | | | 10062223 | Urethral neoplasm |
| | | | | 10066749 | Bladder transitional cell carcinoma stage 0 |
| | | | | 10066750 | Bladder transitional cell carcinoma recurrent |
| | | | | 10066751 | Bladder transitional cell carcinoma stage I |
| | | | | 10066752 | Bladder transitional cell carcinoma stage IV |
| | | | | 10066753 | Bladder transitional cell carcinoma stage II |
| | | | | 10066754 | Bladder transitional cell carcinoma stage III |
| | | | | 10067943 | Hereditary papillary renal carcinoma |
| | | | | 10067944 | Hereditary leiomyomatosis renal cell carcinoma |
| | | | | 10067946 | Renal cell carcinoma |
| | | | | 10069359 | Leukaemic infiltration renal |
| | | | | 10070179 | Denys-Drash syndrome |
| | | | | 10071080 | Transitional cell carcinoma metastatic |
| | | | | 10071664 | Bladder transitional cell carcinoma metastatic |
| | | | | 10072793 | Urethral melanoma metastatic |
| | | | | 10073251 | Clear cell renal cell carcinoma |
| | | | | 10074419 | Malignant genitourinary tract neoplasm |
| | | | | 10077051 | Transitional cell carcinoma recurrent |
| | | | | 10077166 | Genitourinary melanoma |
| | | | | 10078341 | Neuroendocrine carcinoma of the bladder |
| | | | | 10078493 | Papillary renal cell carcinoma |
| | | | | 10080544 | Chromophobe renal cell carcinoma |
| | | | | 10081895 | Multilocular cystic nephroma |
| | | | | 10085663 | Clear cell papillary renal cell carcinoma |
| | | | | 10086817 | Malignant urinary tract neoplasm metastatic |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code Scope | Preferred term code | Preferred term |
|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures (BIcMQ)' | Bone fracture events (BIcMQ) | 40000012 | 10000397 | Acetabulum fracture |
| | | | 10002544 | Ankle fracture |
| | | | 10009245 | Clavicle fracture |
| | | | 10009506 | Closed fracture manipulation |
| | | | 10010149 | Complicated fracture |
| | | | 10010214 | Compression fracture |
| | | | 10015741 | External fixation of fracture |
| | | | 10016042 | Facial bones fracture |
| | | | 10016450 | Femoral neck fracture |
| | | | 10016454 | Femur fracture |
| | | | 10016667 | Fibula fracture |
| | | | 10016747 | Flail chest |
| | | | 10016970 | Foot fracture |
| | | | 10016997 | Forearm fracture |
| | | | 10017076 | Fracture |
| | | | 10017081 | Fracture delayed union |
| | | | 10017085 | Fracture malunion |
| | | | 10017088 | Fracture nonunion |
| | | | 10017107 | Fracture of clavicle due to birth trauma |
| | | | 10017296 | Fractured maxilla elevation |
| | | | 10017308 | Fractured sacrum |
| | | | 10017310 | Fractured skull depressed |
| | | | 10018720 | Greenstick fracture |
| | | | 10019114 | Hand fracture |
| | | | 10020100 | Hip fracture |
| | | | 10020462 | Humerus fracture |
| | | | 10021343 | Ilium fracture |
| | | | 10022576 | Internal fixation of fracture |
| | | | 10023149 | Jaw fracture |
| | | | 10028200 | Multiple fractures |
| | | | 10030527 | Open fracture |
| | | | 10030682 | Open reduction of fracture |
| | | | 10030684 | Open reduction of spinal fracture |
| | | | 10031290 | Osteoporotic fracture |
| | | | 10034122 | Patella fracture |
| | | | 10034156 | Pathological fracture |
| | | | 10037802 | Radius fracture |
| | | | 10039117 | Rib fracture |
| | | | 10039579 | Scapula fracture |
| | | | 10040960 | Skull fractured base |
| | | | 10041541 | Spinal compression fracture |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code Scope | Preferred term code | Preferred term |
|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures (BIcMQ)' | Bone fracture events (BIcMQ) | 40000012 | 10041569 | Spinal fracture |
| | | | 10042015 | Sternal fracture |
| | | | 10042212 | Stress fracture |
| | | | 10043827 | Tibia fracture |
| | | | 10045375 | Ulna fracture |
| | | | 10048049 | Wrist fracture |
| | | | 10048617 | Pseudarthrosis |
| | | | 10049164 | Fractured coccyx |
| | | | 10049514 | Traumatic fracture |
| | | | 10049946 | Cervical vertebral fracture |
| | | | 10049947 | Lumbar vertebral fracture |
| | | | 10049948 | Thoracic vertebral fracture |
| | | | 10052614 | Comminuted fracture |
| | | | 10053206 | Fracture displacement |
| | | | 10053962 | Epiphyseal fracture |
| | | | 10057147 | Fracture debridement |
| | | | 10057609 | Fracture reduction |
| | | | 10059362 | Fractured zygomatic arch elevation |
| | | | 10061161 | Pelvic fracture |
| | | | 10061365 | Skull fracture |
| | | | 10061394 | Upper limb fracture |
| | | | 10061599 | Lower limb fracture |
| | | | 10061959 | Fracture treatment |
| | | | 10064210 | Bone fissure |
| | | | 10064211 | Bone fragmentation |
| | | | 10066094 | Torus fracture |
| | | | 10066184 | Avulsion fracture |
| | | | 10066386 | Impacted fracture |
| | | | 10069066 | Intramedullary rod insertion |
| | | | 10069135 | Periprosthetic fracture |
| | | | 10069723 | Loss of anatomical alignment after fracture reduction |
| | | | 10070884 | Atypical femur fracture |
| | | | 10072132 | Fracture pain |
| | | | 10072395 | Atypical fracture |
| | | | 10073162 | Chance fracture |
| | | | 10073853 | Osteochondral fracture |
| | | | 10074362 | Sacroiliac fracture |
| | | | 10074551 | Limb fracture |
| | | | 10074807 | Spinal fusion fracture |
| | | | 10077270 | Surgical fixation of rib fracture |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Bone fractures (BIcMQ)' | Bone fracture events (BIcMQ) | 40000012 | | 10077603 | Craniofacial fracture |
| | | | | 10078749 | Lisfranc fracture |
| | | | | 10079423 | Fracture blisters |
| | | | | 10079667 | Metaphyseal corner fracture |
| | | | | 10079813 | Fracture infection |
| | | | | 10079864 | Subchondral insufficiency fracture |
| | | | | 10080550 | Osteophyte fracture |
| | | | | 10081343 | Maisonneuve fracture |
| | | | | 10081442 | Stapes fracture |
| | | | | 10083585 | Skull fracture treatment |
| | | | | 10083586 | Spinal fracture treatment |
| | | | | 10085543 | Neurogenic fracture |
| | | | | 10085774 | Microfracture surgery |
| | | | | 10087273 | Depressed fracture |
| Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)' | Genital infections (BIcMQ) | 40000004 | | 10004055 | Bacterial vaginosis |
| | | | | 10004074 | Balanitis candida |
| | | | | 10004078 | Balanoposthitis |
| | | | | 10004138 | Bartholin's abscess |
| | | | | 10004142 | Bartholinitis |
| | | | | 10008323 | Cervicitis |
| | | | | 10014791 | Endometritis |
| | | | | 10015000 | Epididymitis |
| | | | | 10015001 | Epididymitis blastomyces |
| | | | | 10018143 | Genital candidiasis |
| | | | | 10020497 | Hydrocele male infected |
| | | | | 10030345 | Oophoritis |
| | | | | 10031064 | Orchitis |
| | | | | 10033119 | Ovarian abscess |
| | | | | 10033847 | Parametritis |
| | | | | 10034236 | Pelvic abscess |
| | | | | 10034254 | Pelvic inflammatory disease |
| | | | | 10034256 | Pelvic inflammatory disease mycoplasmal |
| | | | | 10034294 | Penile abscess |
| | | | | 10036934 | Prostatic abscess |
| | | | | 10036978 | Prostatitis |
| | | | | 10037651 | Pyometra |
| | | | | 10039453 | Salpingitis |
| | | | | 10039748 | Scrotal gangrene |
| | | | | 10039954 | Seminal vesiculitis |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)' | Genital infections (BIcMQ) | 40000004 | | 10044250 | Toxic shock syndrome staphylococcal |
| | | | | 10044251 | Toxic shock syndrome streptococcal |
| | | | | 10046470 | Urethral stricture post infection |
| | | | | 10046914 | Vaginal infection |
| | | | | 10046957 | Vaginitis gardnerella |
| | | | | 10047732 | Vulval abscess |
| | | | | 10047752 | Vulval cellulitis |
| | | | | 10047780 | Vulvitis |
| | | | | 10047784 | Vulvovaginal candidiasis |
| | | | | 10047794 | Vulvovaginitis |
| | | | | 10048461 | Genital infection |
| | | | | 10049205 | Clitoris abscess |
| | | | | 10049571 | Scrotal abscess |
| | | | | 10049573 | Vaginal abscess |
| | | | | 10049677 | Salpingo-oophoritis |
| | | | | 10050428 | Fallopian tube abscess |
| | | | | 10050662 | Prostate infection |
| | | | | 10050739 | Erosive balanitis |
| | | | | 10051458 | Myometritis |
| | | | | 10051483 | Prostatovesiculitis |
| | | | | 10052301 | Vaginal cellulitis |
| | | | | 10052457 | Perineal abscess |
| | | | | 10053043 | Epididymitis ureaplasmal |
| | | | | 10054259 | Escherichia vaginitis |
| | | | | 10054824 | Tubo-ovarian abscess |
| | | | | 10056254 | Intrauterine infection |
| | | | | 10056345 | Rectovaginal septum abscess |
| | | | | 10056628 | Ovarian bacterial infection |
| | | | | 10057001 | Seminal vesicular infection |
| | | | | 10058674 | Pelvic infection |
| | | | | 10059070 | Pelvic sepsis |
| | | | | 10061179 | Genital infection bacterial |
| | | | | 10061180 | Genital infection fungal |
| | | | | 10061182 | Genitourinary tract infection |
| | | | | 10061912 | Penile infection |
| | | | | 10061977 | Genital infection female |
| | | | | 10062156 | Scrotal infection |
| | | | | 10062233 | Uterine infection |
| | | | | 10062316 | Genital abscess |
| | | | | 10062521 | Genital infection male |
| | | | | 10062707 | Parametric abscess |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Genital tract infections predisposed by glucosuria (BIcMQ)' | Genital infections (BIcMQ) | 40000004 | | 10063012 | Uterine abscess |
| | | | | 10064501 | Spermatic cord funiculitis |
| | | | | 10064724 | Testicular abscess |
| | | | | 10064899 | Vulvovaginal mycotic infection |
| | | | | 10064929 | Cellulitis of male external genital organ |
| | | | | 10065583 | Urogenital infection bacterial |
| | | | | 10066876 | Perineal infection |
| | | | | 10067185 | Vulvovaginitis streptococcal |
| | | | | 10067236 | Cervicitis streptococcal |
| | | | | 10067320 | Prostatitis Escherichia coli |
| | | | | 10067741 | Balanoposthitis infective |
| | | | | 10068682 | Gangrenous balanitis |
| | | | | 10069918 | Bacterial prostatitis |
| | | | | 10071209 | Candida cervicitis |
| | | | | 10072020 | Pyospermia |
| | | | | 10074861 | Endometritis bacterial |
| | | | | 10074997 | Mycoplasma genitalium infection |
| | | | | 10075062 | Cervicitis mycoplasmal |
| | | | | 10075620 | Seminal vesicle abscess |
| | | | | 10078662 | Bacterial salpingitis |
| | | | | 10079520 | Vulvovaginitis staphylococcal |
| | | | | 10079521 | Fungal balanitis |
| | | | | 10079528 | Bacterial vulvovaginitis |
| | | | | 10081280 | Ureaplasmal vulvovaginitis |
| | | | | 10082162 | Ureaplasma cervicitis |
| | | | | 10083412 | Neovaginal infection |
| | | | | 10084348 | Scrotal cellulitis |
| | | | | 10085545 | Penile gangrene |
| Narrow BIcMQ 'Ketoacidosis (BIcMQ)' | Events indicative of ketoacidosis (BIcMQ) | 40000008 | | 10012668 | Diabetic hyperglycaemic coma |
| | | | | 10012671 | Diabetic ketoacidosis |
| | | | | 10012672 | Diabetic ketoacidotic hyperglycaemic coma |
| | | | | 10023379 | Ketoacidosis |
| | | | | 10080061 | Euglycaemic diabetic ketoacidosis |
| Narrow BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis' | Pyelonephritis or Urosepsis (BIcMQ) | 40000013 | | 10023424 | Kidney infection |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Renal infections predisposed by glucosuria (BIcMQ)', PT 'Urosepsis' | Pyelonephritis or Urosepsis (BIcMQ) | 40000013 | | 10034531 | Perinephric abscess |
| | | | | 10037584 | Pyelitis |
| | | | | 10037596 | Pyelonephritis |
| | | | | 10037597 | Pyelonephritis acute |
| | | | | 10037601 | Pyelonephritis chronic |
| | | | | 10037603 | Pyelonephritis mycoplasmal |
| | | | | 10037653 | Pyonephrosis |
| | | | | 10038351 | Renal abscess |
| | | | | 10048709 | Urosepsis |
| | | | | 10049100 | Pyelocystitis |
| | | | | 10058596 | Renal cyst infection |
| | | | | 10059517 | Bacterial pyelonephritis |
| | | | | 10065214 | Pyelonephritis fungal |
| | | | | 10068822 | Emphysematous pyelonephritis |
| | | | | 10072058 | Perinephritis |
| | | | | 10074409 | Escherichia pyelonephritis |
| | | | | 10078229 | Renal graft infection |
| | | | | 10082040 | Nephritis bacterial |
| | | | | 10084121 | Infected urinoma |
| Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)' | Urinary tract infections (BIcMQ) | 40000002 | | 10004056 | Bacteriuria |
| | | | | 10004058 | Bacteriuria in pregnancy |
| | | | | 10011781 | Cystitis |
| | | | | 10011790 | Cystitis escherichia |
| | | | | 10011792 | Cystitis gonococcal |
| | | | | 10011793 | Cystitis haemorrhagic |
| | | | | 10011797 | Cystitis klebsiella |
| | | | | 10011799 | Cystitis pseudomonal |
| | | | | 10017525 | Fungal cystitis |
| | | | | 10023424 | Kidney infection |
| | | | | 10034531 | Perinephric abscess |
| | | | | 10037584 | Pyelitis |
| | | | | 10037596 | Pyelonephritis |
| | | | | 10037597 | Pyelonephritis acute |
| | | | | 10037601 | Pyelonephritis chronic |
| | | | | 10037603 | Pyelonephritis mycoplasmal |
| | | | | 10037653 | Pyonephrosis |
| | | | | 10038351 | Renal abscess |
| | | | | 10046424 | Urethral abscess |
| | | | | 10046470 | Urethral stricture post infection |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)' | Urinary tract infections (BIcMQ) | 40000002 | | 10046480 | Urethritis |
| | | | | 10046482 | Urethritis chlamydial |
| | | | | 10046483 | Urethritis gonococcal |
| | | | | 10046489 | Urethritis trichomonal |
| | | | | 10046490 | Urethritis ureaplasmal |
| | | | | 10046571 | Urinary tract infection |
| | | | | 10046572 | Urinary tract infection enterococcal |
| | | | | 10046573 | Urinary tract infection neonatal |
| | | | | 10046704 | Urogenital trichomoniasis |
| | | | | 10048709 | Urosepsis |
| | | | | 10049059 | Urinary tract infection fungal |
| | | | | 10049100 | Pyelocystitis |
| | | | | 10051250 | Ureteritis |
| | | | | 10051959 | Urinary bladder abscess |
| | | | | 10052238 | Escherichia urinary tract infection |
| | | | | 10052299 | Urethral carbuncle |
| | | | | 10054088 | Urinary tract infection bacterial |
| | | | | 10056351 | Emphysematous cystitis |
| | | | | 10056396 | Asymptomatic bacteriuria |
| | | | | 10058523 | Bladder candidiasis |
| | | | | 10058596 | Renal cyst infection |
| | | | | 10059517 | Bacterial pyelonephritis |
| | | | | 10061181 | Genitourinary tract gonococcal infection |
| | | | | 10061395 | Ureter abscess |
| | | | | 10062279 | Urinary tract infection pseudomonal |
| | | | | 10062280 | Urinary tract infection staphylococcal |
| | | | | 10064850 | Cystitis erosive |
| | | | | 10065198 | Cystitis bacterial |
| | | | | 10065214 | Pyelonephritis fungal |
| | | | | 10065582 | Urogenital infection fungal |
| | | | | 10065583 | Urogenital infection bacterial |
| | | | | 10066757 | Urinary tract abscess |
| | | | | 10068822 | Emphysematous pyelonephritis |
| | | | | 10070300 | Streptococcal urinary tract infection |
| | | | | 10072058 | Perinephritis |
| | | | | 10074409 | Escherichia pyelonephritis |
| | | | | 10074457 | Bladder diverticulitis |
| | | | | 10075063 | Urethritis mycoplasmal |
| | | | | 10077375 | Funguria |
| | | | | 10078229 | Renal graft infection |
| | | | | 10078665 | Bacterial urethritis |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'UTI predisposed by glucosuria (BIcMQ)' | Urinary tract infections (BIcMQ) | 40000002 | | 10078666 | Bacterial ureteritis |
| | | | | 10081163 | Fungal urethritis |
| | | | | 10081185 | Gonococcal infection |
| | | | | 10081262 | Candida urethritis |
| | | | | 10082040 | Nephritis bacterial |
| | | | | 10082818 | Providencia urinary tract infection |
| | | | | 10083162 | Urinary tract candidiasis |
| | | | | 10083524 | Campylobacter urinary tract infection |
| | | | | 10084121 | Infected urinoma |
| | | | | 10084826 | Aerococcus urinae infection |
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)' | Volume depletion events (BIcMQ) | 40000006 | | 10005731 | Blood pressure ambulatory decreased |
| | | | | 10005734 | Blood pressure decreased |
| | | | | 10005737 | Blood pressure diastolic decreased |
| | | | | 10005758 | Blood pressure systolic decreased |
| | | | | 10009192 | Circulatory collapse |
| | | | | 10012174 | Dehydration |
| | | | | 10021097 | Hypotension |
| | | | | 10021137 | Hypovolaemia |
| | | | | 10021138 | Hypovolaemic shock |
| | | | | 10026983 | Mean arterial pressure decreased |
| | | | | 10031127 | Orthostatic hypotension |
| | | | | 10036653 | Presyncope |
| | | | | 10042772 | Syncope |
| | | | | 10053356 | Blood pressure orthostatic decreased |
| | | | | 10066077 | Diastolic hypotension |
| | | | | 10078280 | CT hypotension complex |
| | | | | 10083659 | Hypotensive crisis |
| | | | | 10084012 | Dialysis hypotension |
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)' excluding PTs 'Dehydration' and 'Hypovolaemia' | Hypotension events (BIcMQ) | 40000001 | | 10005731 | Blood pressure ambulatory decreased |
| | | | | 10005734 | Blood pressure decreased |
| | | | | 10005737 | Blood pressure diastolic decreased |
| | | | | 10005758 | Blood pressure systolic decreased |
| | | | | 10009192 | Circulatory collapse |
| | | | | 10021097 | Hypotension |
| | | | | 10021138 | Hypovolaemic shock |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow BIcMQ 'Volume depletion and hypotension due to dehydration (BIcMQ)' excluding PTs 'Dehydration' and 'Hypovolaemia' | Hypotension events (BIcMQ) | 40000001 | | 10026983 | Mean arterial pressure decreased |
| | | | | 10031127 | Orthostatic hypotension |
| | | | | 10036653 | Presyncope |
| | | | | 10042772 | Syncope |
| | | | | 10053356 | Blood pressure orthostatic decreased |
| | | | | 10066077 | Diastolic hypotension |
| | | | | 10078280 | CT hypotension complex |
| | | | | 10083659 | Hypotensive crisis |
| | | | | 10084012 | Dialysis hypotension |
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10000804 | Acute hepatic failure |
| | | | | 10001547 | Alanine aminotransferase abnormal |
| | | | | 10001551 | Alanine aminotransferase increased |
| | | | | 10001942 | Ammonia abnormal |
| | | | | 10001946 | Ammonia increased |
| | | | | 10003445 | Ascites |
| | | | | 10003477 | Aspartate aminotransferase abnormal |
| | | | | 10003481 | Aspartate aminotransferase increased |
| | | | | 10003547 | Asterixis |
| | | | | 10003827 | Autoimmune hepatitis |
| | | | | 10004659 | Biliary cirrhosis |
| | | | | 10004664 | Biliary fibrosis |
| | | | | 10004685 | Bilirubin conjugated increased |
| | | | | 10004792 | Biopsy liver abnormal |
| | | | | 10005364 | Blood bilirubin increased |
| | | | | 10005370 | Blood bilirubin unconjugated increased |
| | | | | 10006408 | Bromosulphthalein test abnormal |
| | | | | 10008635 | Cholestasis |
| | | | | 10008909 | Chronic hepatitis |
| | | | | 10010075 | Coma hepatic |
| | | | | 10017688 | Gamma-glutamyltransferase abnormal |
| | | | | 10017693 | Gamma-glutamyltransferase increased |
| | | | | 10019621 | Hepaplastin abnormal |
| | | | | 10019622 | Hepaplastin decreased |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
MedDRA version: 25.0

Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10019637 | Hepatic atrophy |
| | | | | 10019641 | Hepatic cirrhosis |
| | | | | 10019660 | Hepatic encephalopathy |
| | | | | 10019663 | Hepatic failure |
| | | | | 10019668 | Hepatic fibrosis |
| | | | | 10019670 | Hepatic function abnormal |
| | | | | 10019692 | Hepatic necrosis |
| | | | | 10019705 | Hepatic pain |
| | | | | 10019708 | Hepatic steatosis |
| | | | | 10019717 | Hepatitis |
| | | | | 10019727 | Hepatitis acute |
| | | | | 10019754 | Hepatitis cholestatic |
| | | | | 10019755 | Hepatitis chronic active |
| | | | | 10019759 | Hepatitis chronic persistent |
| | | | | 10019772 | Hepatitis fulminant |
| | | | | 10019795 | Hepatitis toxic |
| | | | | 10019837 | Hepatocellular injury |
| | | | | 10019842 | Hepatomegaly |
| | | | | 10019845 | Hepatorenal failure |
| | | | | 10019846 | Hepatorenal syndrome |
| | | | | 10019847 | Hepatosplenomegaly |
| | | | | 10019851 | Hepatotoxicity |
| | | | | 10020575 | Hyperammonaemia |
| | | | | 10020578 | Hyperbilirubinaemia |
| | | | | 10021209 | Icterus index increased |
| | | | | 10023025 | Ischaemic hepatitis |
| | | | | 10023126 | Jaundice |
| | | | | 10023129 | Jaundice cholestatic |
| | | | | 10023136 | Jaundice hepatocellular |
| | | | | 10023321 | Kayser-Fleischer ring |
| | | | | 10024670 | Liver disorder |
| | | | | 10024690 | Liver function test abnormal |
| | | | | 10024712 | Liver tenderness |
| | | | | 10024714 | Liver transplant |
| | | | | 10025129 | Lupoid hepatic cirrhosis |
| | | | | 10029530 | Non-alcoholic fatty liver |
| | | | | 10030210 | Oesophageal varices haemorrhage |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10036200 | Portal hypertension |
| | | | | 10039012 | Reye's syndrome |
| | | | | 10045428 | Ultrasound liver abnormal |
| | | | | 10048611 | Cholaemia |
| | | | | 10049199 | Hepatic cytolysis |
| | | | | 10049631 | Oedema due to hepatic disease |
| | | | | 10050792 | Urine bilirubin increased |
| | | | | 10050897 | Portal hypertensive gastropathy |
| | | | | 10051010 | Duodenal varices |
| | | | | 10051012 | Gastric varices |
| | | | | 10051015 | Radiation hepatitis |
| | | | | 10051081 | Nodular regenerative hyperplasia |
| | | | | 10051333 | Guanase increased |
| | | | | 10051343 | Bile output decreased |
| | | | | 10051344 | Bile output abnormal |
| | | | | 10051924 | Hypercholia |
| | | | | 10052274 | Hepatopulmonary syndrome |
| | | | | 10052279 | Renal and liver transplant |
| | | | | 10052550 | Liver induration |
| | | | | 10052554 | Foetor hepaticus |
| | | | | 10053219 | Non-alcoholic steatohepatitis |
| | | | | 10053244 | Hepatocellular foamy cell syndrome |
| | | | | 10054125 | Perihepatic discomfort |
| | | | | 10054889 | Transaminases increased |
| | | | | 10056091 | Varices oesophageal |
| | | | | 10056536 | X-ray hepatobiliary abnormal |
| | | | | 10056956 | Subacute hepatic failure |
| | | | | 10057110 | Hepatic mass |
| | | | | 10057572 | Gastric varices haemorrhage |
| | | | | 10057573 | Chronic hepatic failure |
| | | | | 10058117 | Ocular icterus |
| | | | | 10058477 | Blood bilirubin abnormal |
| | | | | 10059710 | Galactose elimination capacity test abnormal |
| | | | | 10059712 | Galactose elimination capacity test decreased |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10060107 | Liver-kidney microsomal antibody positive |
| | | | | 10060794 | Hepatic enzyme decreased |
| | | | | 10060795 | Hepatic enzyme increased |
| | | | | 10061009 | Bilirubin excretion disorder |
| | | | | 10061135 | Spontaneous bacterial peritonitis |
| | | | | 10061947 | Liver scan abnormal |
| | | | | 10061997 | Hepatectomy |
| | | | | 10061998 | Hepatic lesion |
| | | | | 10062000 | Hepatobiliary disease |
| | | | | 10062040 | Liver operation |
| | | | | 10062685 | Hepatic enzyme abnormal |
| | | | | 10062688 | Transaminases abnormal |
| | | | | 10063075 | Cryptogenic cirrhosis |
| | | | | 10064190 | Cholestatic pruritus |
| | | | | 10064558 | Total bile acids increased |
| | | | | 10064668 | Hepatic infiltration eosinophilic |
| | | | | 10064676 | Graft versus host disease in liver |
| | | | | 10064712 | Mitochondrial aspartate aminotransferase increased |
| | | | | 10065274 | Hepatic calcification |
| | | | | 10066195 | Hepatobiliary scan abnormal |
| | | | | 10066244 | Hepatic sequestration |
| | | | | 10066263 | Acute graft versus host disease in liver |
| | | | | 10066597 | Gastrooesophageal variceal haemorrhage prophylaxis |
| | | | | 10066599 | Hepatic encephalopathy prophylaxis |
| | | | | 10066758 | Mixed liver injury |
| | | | | 10066869 | Molar ratio of total branched-chain amino acid to tyrosine |
| | | | | 10067125 | Liver injury |
| | | | | 10067281 | Portopulmonary hypertension |
| | | | | 10067338 | Retrograde portal vein flow |
| | | | | 10067365 | Hepatic hydrothorax |
| | | | | 10067718 | Bilirubin conjugated abnormal |
| | | | | 10067737 | Lupus hepatitis |
| | | | | 10067823 | Splenic varices |
| | | | | 10067969 | Cholestatic liver injury |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BIcMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10068237 | Hypertransaminasaemia |
| | | | | 10068287 | Child-Pugh-Turcotte score increased |
| | | | | 10068358 | Hepatic vascular resistance increased |
| | | | | 10068547 | Bacterascites |
| | | | | 10068662 | Splenic varices haemorrhage |
| | | | | 10068923 | Portal hypertensive enteropathy |
| | | | | 10068997 | Hepatic artery flow decreased |
| | | | | 10070815 | Acute yellow liver atrophy |
| | | | | 10070953 | Reynold's syndrome |
| | | | | 10071198 | Allergic hepatitis |
| | | | | 10071265 | Diabetic hepatopathy |
| | | | | 10071502 | Intestinal varices |
| | | | | 10072160 | Chronic graft versus host disease in liver |
| | | | | 10072268 | Drug-induced liver injury |
| | | | | 10072284 | Varicose veins of abdominal wall |
| | | | | 10072319 | Gallbladder varices |
| | | | | 10073209 | Portal vein dilatation |
| | | | | 10073215 | Peripancreatic varices |
| | | | | 10073979 | Portal vein cavernous transformation |
| | | | | 10074150 | Biliary ascites |
| | | | | 10074151 | Parenteral nutrition associated liver disease |
| | | | | 10074726 | Portal fibrosis |
| | | | | 10075895 | Liver palpable |
| | | | | 10076237 | Gastric variceal injection |
| | | | | 10076238 | Gastric variceal ligation |
| | | | | 10076254 | Hepatic hypertrophy |
| | | | | 10076331 | Steatohepatitis |
| | | | | 10076640 | Liver dialysis |
| | | | | 10077020 | Child-Pugh-Turcotte score abnormal |
| | | | | 10077215 | Hepatic steato-fibrosis |
| | | | | 10077259 | Non-cirrhotic portal hypertension |
| | | | | 10077305 | Acute on chronic liver failure |
| | | | | 10077356 | Bilirubin urine present |
| | | | | 10077677 | Liver function test decreased |
| | | | | 10077692 | Liver function test increased |

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Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BICMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| Narrow SMQs 'Liver related investigations, signs and symptoms', 'Cholestasis and jaundice of hepatic origin', 'Hepatitis, non-infectious', 'Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions' | Hepatic events (SMQ) | 40000011 | | 10078058 | Intestinal varices haemorrhage |
| | | | | 10078360 | Computerised tomogram liver abnormal |
| | | | | 10078438 | White nipple sign |
| | | | | 10078962 | Immune-mediated hepatitis |
| | | | | 10079446 | Portal hypertensive colopathy |
| | | | | 10080429 | Primary biliary cholangitis |
| | | | | 10080576 | Alloimmune hepatitis |
| | | | | 10080679 | Regenerative siderotic hepatic nodule |
| | | | | 10080860 | Acquired hepatocerebral degeneration |
| | | | | 10082443 | Magnetic resonance proton density fat fraction measurement |
| | | | | 10082480 | Cardiohepatic syndrome |
| | | | | 10082832 | AST/ALT ratio abnormal |
| | | | | 10083010 | Sugiura procedure |
| | | | | 10083171 | Hepatic venous pressure gradient increased |
| | | | | 10083172 | Hepatic venous pressure gradient abnormal |
| | | | | 10083406 | Immune-mediated cholangitis |
| | | | | 10083521 | Immune-mediated hepatic disorder |
| | | | | 10084058 | Congestive hepatopathy |
| | | | | 10084751 | Hepatic hypoperfusion |
| | | | | 10084797 | Flood syndrome |
| | | | | 10085121 | Magnetic resonance imaging hepatobiliary abnormal |
| | | | | 10086006 | Acquired factor V deficiency |
| | | | | 10086970 | Anti-liver cytosol antibody type 1 positive |
| | | | | 10087030 | Omental oedema |
| PTs 'Gout', 'Gouty arthritis', 'Gouty tophus' | Gout (user-defined) | 40000032 | | 10018627 | Gout |
| | | | | 10018634 | Gouty arthritis |
| | | | | 10018641 | Gouty tophus |
| PTs 'Hyperkalaemia', 'Blood potassium increased' | Hyperkalaemia (user-defined) | 40000021 | | 10005725 | Blood potassium increased |

Analyses are based on pooled 1245.110 and 1245.121 CKD subpopulations (patients with eGFR < 60 and/or UACR >= 30 at baseline).
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Listing R.5.2.6: 1 Preferred terms that define adverse events of special interest and other specific AE categories defined via BICMQ, SMQs or user-defined searches

| Source | Group | Group code | Scope | Preferred term code | Preferred term |
|---|---|---|---|---|---|
| PTs 'Hyperkalaemia', 'Blood potassium increased' | Hyperkalaemia (user-defined) | 40000021 | | 10020646 | Hyperkalaemia |
| SMQ 'Acute renal failure' | Acute renal failure (SMQ) | 20000003 | Narrow | 10002847 | Anuria |
| | | | | 10003885 | Azotaemia |
| | | | | 10018875 | Haemodialysis |
| | | | | 10029155 | Nephropathy toxic |
| | | | | 10030302 | Oliguria |
| | | | | 10034660 | Peritoneal dialysis |
| | | | | 10038435 | Renal failure |
| | | | | 10038447 | Renal failure neonatal |
| | | | | 10049776 | Renal impairment neonatal |
| | | | | 10049778 | Neonatal anuria |
| | | | | 10053090 | Haemofiltration |
| | | | | 10061105 | Dialysis |
| | | | | 10062237 | Renal impairment |
| | | | | 10066338 | Continuous haemodiafiltration |
| | | | | 10069339 | Acute kidney injury |
| | | | | 10069688 | Acute phosphate nephropathy |
| | | | | 10072370 | Prerenal failure |
| | | | | 10078987 | Foetal renal impairment |
| | | | | 10081980 | Subacute kidney injury |
| SMQ 'Hypoglycaemia' | Hypoglycaemic events (SMQ) | 20000226 | Narrow | 10005555 | Blood glucose decreased |
| | | | | 10020993 | Hypoglycaemia |
| | | | | 10020994 | Hypoglycaemia neonatal |
| | | | | 10020997 | Hypoglycaemia unawareness |
| | | | | 10021000 | Hypoglycaemic coma |
| | | | | 10021002 | Hypoglycaemic encephalopathy |
| | | | | 10040576 | Shock hypoglycaemic |
| | | | | 10048803 | Hypoglycaemic seizure |
| | | | | 10054998 | Neuroglycopenia |
| | | | | 10059035 | Postprandial hypoglycaemia |
| | | | | 10065981 | Hypoglycaemic unconsciousness |
| | | | | 10077216 | Hyperinsulinaemic hypoglycaemia |
| | | | | 10080024 | Nesidioblastosis |
| | | | | 10082152 | Paraneoplastic hypoglycaemia |
| | | | | 10082172 | Glycopenia |

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MedDRA version: 25.0